F. ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 May 2001 (16.05.01)	
International application No. PCT/EP00/08882	**Applicant's or agent's file reference** E SD/RS/XJ19/47
International filing date (day/month/year) 08 September 2000 (08.09.00)	**Priority date** (day/month/year) 10 September 1999 (10.09.99)
Applicant HERDEWIJN, Piet et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 March 2001 (27.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

P ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and Administrative Instructions, Sections 402 and 409)

To:

DUXBURY, Stephen
Arnold & Siedsma
Sweelinckplein 1
NL-2517 GK The Hague
BELGIQUE

Date of mailing (day/month/year)
17 January 2001 (17.01.01)

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
E SD/RS/XJ19/47

International application No.
PCT/EP00/08882

International filing date (day/month/year)
08 September 2000 (08.09.00)

Applicant
STICHTING REGA VZW et al

The applicant is hereby **notified** of the following in respect of the priority claim(s) made in the international application.

1. [X] **Correction of priority claim.** In accordance with the applicant's notice received on: 04 January 2001 (04.01.01), the following priority claim has been corrected to read as follows:

US 10 September 1999 (10.09.99) 60/153,087

[ ] even though the indication of the number of the earlier application is missing.
[ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

2. [ ] **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:

[ ] even though the indication of the number of the earlier application is missing.
[ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

3. [ ] As a **result of the correction and/or addition** of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:

4. [ ] **Priority claim considered not to have been made.**
[ ] The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
[ ] The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
[ ] The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.
The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(IB).

5. [ ] In case where **multiple priorities** have been claimed, the above item(s) relate to the following priority claim(s):

6. A copy of this notification has been sent to the receiving Office and
[X] to the International Searching Authority (where the international search report has not yet been issued).
[X] the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
Dominique DELMAS

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
E SD/RS/XJ19/47		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08882	08/09/2000	10/09/1999
International Patent Classification (IPC) or national classification and IPC C07D473/32		
Applicant STICHTING REGA VZW et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/03/2001	10.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wolf, C Telephone No. +49 89 2399 8285

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08882

I. Basis of the r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-40 as originally filed

Claims, No.:

1-43 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 40-42 IN RESPECT OF INDUSTRIAL APPLICABILITY.

because:

☒ the said international application, or the said claims Nos. 40-42 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-43

	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-43
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-39, 43
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

1. D1: WO 93 25565 A (STICHTING REGA V Z W ;CLERCQ ERIK DESIRE ALICE DE (BE); HERDEWIJN) 23 December 1993 (1993-12-23)
   D2: WO 93 17020 A (WELLCOME FOUND) 2 September 1993 (1993-09-02)
   D3: WO 91 15488 A (FROUD CLIVE ;NYCOMED AS (NO)) 17 October 1991 (1991-10-17)
   D4: GB-A-2 097 785 (BRISTOL MYERS CO) 10 November 1982 (1982-11-10)
   D5: GB-A-2 020 655 (BRISTOL MYERS CO) 21 November 1979 (1979-11-21)
   D6: G. H. POSNER ET AL: 'Highly stereocontrolledsynthesis of some trioxygenated cyclohexenes: an asymmetric total synthesis of (-)-methyl-triacetyl-4-epishikimate' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 108, no. 23, 1986, pages 7373-7377, XP002157745 DC US
   D7: J. WANG ET AL: 'Enantioselective synthesis and conformational study of cyclohexene carbocyclic nucleosides' JOURNAL OF ORGANIC CHEMISTRY, vol. 64, no. 21, 15 October 1999 (1999-10-15), pages 7820-7827, XP002157746 EASTON US
   D8: J. WANG ET AL: 'The cyclohexene ring system as a furanose mimic: synthesis and antiviral activity of both enantiomers of cyclohexenylguanine' JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 4, 24 February 2000 (2000-02-24), pages 736-745, XP002157747 WASHINGTON US

D7 and D8 will not be considered at this stage, since they are not prepublished to the priority date of the present application and it is assumed that the priority has been validly claimed (see section III).

D1 discloses antiviral effective compounds which differ from the claimed compounds mainly in that the six-membered nucleoside analogue has an oxygen ring atom and the compounds as claimed in the present application have a six-membered carbocyclic moiety.

D2 and D3 disclose antiviral effective compounds which differ structurally mainly from the compounds of the present application in that they exhibit a five-membered carbocyclic portion.

D4, D5 and D6 disclose structurally different compounds which do not exhibit antiviral activity.

The compounds as claimed appear to be novel in the light of the cited relevant prior art (Article 33(2) PCT, section V).

2. The technical problem underlying the present application was the provision of further compounds useful as antiviral agents (Article 33(3) PCT, section V).

A skilled person faced with the task of solving said technical problem would not have arrived at the claimed compounds without inventive ingenuity. The antiviral compounds as claimed exhibit a six-membered carbocyclic moiety. The antiviral compounds of D1 exhibit an oxygen ring atom atom containing carbocyclic moiety and the compounds of D2 exhibit a five-membered carbocyclic moiety. The technical teachings of D1 and D2 cannot be combined structurally without one additional structural step to be taken by the skilled person to arrive at the compounds as claimed in the present application. The solution of the technical problem appears to be non-obvious in the light of D1 and D2 and thus the subject matter claimed appears to involve an inventive step (Article 33(3) PCT).

3. For the assessment of the present claims 40-42 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 40-42 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
E SD/RS/XJ19/47		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 08882	08/09/2000	10/09/1999
Applicant		
STICHTING REGA VZW et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
[redacted]/EP 00/08882

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D473/32 C07D473/18 C07D473/34 C07D239/46 C07C43/188
C07C35/18 C07F7/18 A61K31/52 A61K31/522 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 25565 A (STICHTING REGA V Z W ;CLERCQ ERIK DESIRE ALICE DE (BE); HERDEWIJN) 23 December 1993 (1993-12-23) claims	1-43
Y	WO 93 17020 A (WELLCOME FOUND) 2 September 1993 (1993-09-02) claims	1-43
Y	WO 91 15488 A (FROUD CLIVE ;NYCOMED AS (NO)) 17 October 1991 (1991-10-17) claims	1-43
A	GB 2 097 785 A (BRISTOL MYERS CO) 10 November 1982 (1982-11-10) claims	1-43

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2001	05/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 020 655 A (BRISTOL MYERS CO) 21 November 1979 (1979-11-21) claims	1-43
A	G. H. POSNER ET AL: "Highly stereocontrolledsynthesis of some trioxygenated cyclohexenes: an asymmetric total synthesis of (-)-methyl-triacetyl-4-epishikimate" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 108, no. 23, 1986, pages 7373-7377, XP002157745 DC US the whole document	26,27
P,X	J. WANG ET AL: "Enantioselective synthesis and conformational study of cyclohexene carbocyclic nucleosides" JOURNAL OF ORGANIC CHEMISTRY, vol. 64, no. 21, 15 October 1999 (1999-10-15), pages 7820-7827, XP002157746 EASTON US the whole document	1-43
P,X	J. WANG ET AL: "The cyclohexene ring system as a furanose mimic: synthesis and antiviral activity of both enantiomers of cyclohexenylguanine" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 4, 24 February 2000 (2000-02-24), pages 736-745, XP002157747 WASHINGTON US the whole document	1-43

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/08882

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9325565 A	23-12-1993	AT 166655 T	15-06-1998
		AU 671129 B	15-08-1996
		AU 4301393 A	04-01-1994
		CA 2138415 A	23-12-1993
		DE 69318836 D	02-07-1998
		DE 69318836 T	28-01-1999
		DK 646125 T	22-03-1999
		EP 0646125 A	05-04-1995
		ES 2117134 T	01-08-1998
		GR 3027651 T	30-11-1998
		JP 8501071 T	06-02-1996
		NL 9300058 A	17-01-1994
		US 5607922 A	04-03-1997
		US 5668113 A	16-09-1997
WO 9317020 A	02-09-1993	AU 707075 B	01-07-1999
		AU 2489197 A	28-08-1997
		AU 3571093 A	13-09-1993
		EP 0628044 A	14-12-1994
		JP 7504185 T	11-05-1995
		US 5641889 A	24-06-1997
		US 5840990 A	24-11-1998
		US 5919941 A	06-07-1999
		US 5808147 A	15-09-1998
WO 9115488 A	17-10-1991	AU 7695991 A	30-10-1991
		EP 0523160 A	20-01-1993
		NO 923848 A	03-12-1992
		OA 9670 A	15-05-1993
GB 2097785 A	10-11-1982	US 4172829 A	30-10-1979
		AU 532056 B	15-09-1983
		AU 4689679 A	15-11-1979
		BE 876122 A	08-11-1979
		CA 1109871 A	29-09-1981
		CA 1109872 A	29-09-1981
		CH 640534 A	13-01-1984
		DE 2918261 A	15-11-1979
		DK 188279 A,B,	10-11-1979
		DK 461480 A,B,	30-10-1980
		FI 791456 A,B,	10-11-1979
		FI 841219 A,B,	27-03-1984
		FI 851713 A,B,	30-04-1985
		FR 2432519 A	29-02-1980
		FR 2429793 A	25-01-1980
		GB 2020655 A,B	21-11-1979
		GR 73535 A	12-03-1984
		IE 48216 B	31-10-1984
		IE 48217 B	31-10-1984
		IT 1116833 B	10-02-1986
		JP 1400188 C	28-09-1987
		JP 55000373 A	05-01-1980
		JP 62006555 B	12-02-1987
		JP 1046515 B	09-10-1989
		JP 1563633 C	12-06-1990
		JP 62116583 A	28-05-1987
		LU 81238 A	07-12-1979
		NL 7903650 A	13-11-1979

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/08882

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2097785 A		SE 436033 B	05-11-1984
		SE 7903976 A	10-11-1979
		SE 449864 B	25-05-1987
		SE 8401493 A	16-03-1984
		US 4201860 A	06-05-1980
		YU 108579 A	31-12-1983
		ZA 7902186 A	28-05-1980
GB 2020655 A	21-11-1979	US 4172829 A	30-10-1979
		AU 532056 B	15-09-1983
		AU 4689679 A	15-11-1979
		BE 876122 A	08-11-1979
		CA 1109871 A	29-09-1981
		CA 1109872 A	29-09-1981
		CH 640534 A	13-01-1984
		DE 2918261 A	15-11-1979
		DK 188279 A,B,	10-11-1979
		DK 461480 A,B,	30-10-1980
		FI 791456 A,B,	10-11-1979
		FI 841219 A,B,	27-03-1984
		FI 851713 A,B,	30-04-1985
		FR 2432519 A	29-02-1980
		FR 2429793 A	25-01-1980
		GB 2097785 A,B	10-11-1982
		GR 73535 A	12-03-1984
		IE 48216 B	31-10-1984
		IE 48217 B	31-10-1984
		IT 1116833 B	10-02-1986
		JP 1400188 C	28-09-1987
		JP 55000373 A	05-01-1980
		JP 62006555 B	12-02-1987
		JP 1046515 B	09-10-1989
		JP 1563633 C	12-06-1990
		JP 62116583 A	28-05-1987
		LU 81238 A	07-12-1979
		NL 7903650 A	13-11-1979
		SE 436033 B	05-11-1984
		SE 7903976 A	10-11-1979
		SE 449864 B	25-05-1987
		SE 8401493 A	16-03-1984
		US 4201860 A	06-05-1980
		YU 108579 A	31-12-1983
		ZA 7902186 A	28-05-1980

1. the Declaration and Power of Attorney; and

2. a copy of the above-mentioned "Notification" to be returned with response.

Regarding additional claims fees, the undersigned has calculated the claims and fees as follows:

$504 for 9 independent claims over 3.
$522 for 29 total claims over 20.
$280 for multiple dependent claims surcharge.

Total fees required: $1306. Because Applicants' previously paid additional claims fees in the amount of $666, it is believed that additional claim fees in the amount of $640 are due. It is respectfully requested that the claim fees be recalculated and that the accompanying check in the amount of $640 be accepted as final payment of all filing fees.

The Commissioner for Patents is hereby authorized to charge any additional fees as set forth in 37 CFR 1.16 and 1.17 which may be required, or credit any overpayment to Deposit Account No. 23-0650. The original and two copies of this Letter are enclosed.

Respectfully submitted,

WEBB ZIESENHEIM LOGSDON
ORKIN & HANSON, P.C.

By _____

Barbara E. Johnson
Registration No. 31,198
Attorney for Applicants
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219-1818
Telephone: 412-471-8815
Facsimile: 412-471-4094

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/18003 A1

(51) International Patent Classification[7]: C07D 473/32, 473/18, 473/34, 239/46, C07C 43/188, 35/18, C07F 7/18, A61K 31/52, 31/522, A61P 31/12

(21) International Application Number: PCT/EP00/08882

(22) International Filing Date:
8 September 2000 (08.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/153,086	10 September 1999 (10.09.1999)	US
60/153,087	10 September 1999 (10.09.1999)	US
60/214,897	29 June 2000 (29.06.2000)	US

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(72) Inventors; and

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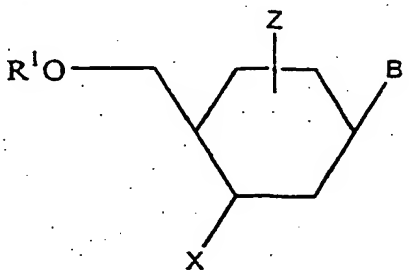
(54) Title: CARBOCYCLIC NUCLEOSIDES AND PROCESS FOR OBTAINING SUCH



(I)

(57) Abstract: A six membered, at least partially unsaturated, carbocyclic nucleoside compound, including the (-) enantiomer, the (+) enantiomer, and pharmaceutically acceptable salts and esters thereof, the compounds represented by general formula (I) wherein: Z represents the presence of 1 or more double bonds in the six membered carbocyclic ring, B is a heterocyclic ring selected from the group consisting of pyrimidine and purine bases, X is a hydrogen, azido, F, or OR^2, R^1 and R^2 are the same or different and represent the same or different protecting groups, hydrogen, alkyl, alkenyl, acyl or phosphate moieties wherein; the alkyl moiety is a saturated, substituted or unsubsituted straight or branched chains hydrocarbon radical having from 1 to 20, for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms, the alkenyl moiety is an unsaturated congener of the alkyl group and, the acyl moiety is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl substituted benzoyl or naphtoyl.

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CARBOCYCLIC NUCLEOSIDES AND PROCESS FOR OBTAINING SUCH

The invention relates to carbocyclic nucleoside analogues and their pharmaceutically acceptable salts, and to a method for the production of such, and to their use as anti-viral agents, amongst others.

Most antiviral compounds belong to the nucleoside field and the development of new modified nucleosides as antiviral agents is an active field of research. An object of the present invention is to provide an agent exhibiting pharmaceutical activity.

According to a first aspect of the present invention there is provided a carbocyclic nucleoside analogue as described in claims 1-14.

These carbocyclic nucleotides exhibit good pharmaceutical activity.

According to a second aspect of the present invention there is provided a process for providing these carbocyclic compounds and intermediates thereof according to claims 15-24.

According to a further aspect of the present invention there is provided a carbocyclic compound according to any of the claims 24-35.

According to a further aspect of the present invention there is provided a pharmaceutical composition and the use of such, according to the claims 36-39.

Further aspects of the invention are detailed in claims 40-43.

The inventors have developed an enantioselective approach toward the synthesis of (D)-cyclohexene nucleoside **4** (Figure 3) using R-(-)-carvone (1) as inexpensive starting material. A sequence of chemical transformations led to intermediate 2, possessing four chiral centers and, disregarding the protecting groups R_1-R_4, a plane of symmetry. Intermediate

2 allows for the synthesis of both the (D)- and the (L)-cyclohexene nucleosides **4** and **5**, and **7** and **8**, respectively.

The synthesis of (D)-adenine cyclohexene nucleoside **4** was accomplished by using a Mitsunobu type reaction on enol **3** to introduce the adenine base moiety on the cyclohexenyl ring. The corresponding guanine derivative **5** was synthesized in a similar way. Enol **3** was reacted with 2-amino-6-chloropurine in the presence of DEAD and triphenyl phosphine in dioxane to give **9** (Figure 4), which was converted to **5** by treatment with TFA-H_2O 3:1. Under these reaction conditions the two TBDMS protecting groups were simultaneously removed. The overall yield starting from **3** was 46%. Analytically pure **5** was obtained by reversed-phase HPLC purification.

The synthesis of the (L)-cyclohexene nucleosides **7** and **8** was carried out by protection of the C4-CH_2OH and C5-OH groups (**2b**), followed by conversion of the OR_2 and OR_4 groups into enol **6**. This compound was then used for the introduction of the base moiety according to the same strategy as used for the (D)-series. Intermediate **2b** ($R_1 = R_3 = H$; $R_2 = R_4 =$ TBDMS) was converted to dibenzoate **10** (Figure 5) using standard reaction conditions (Bz_2O, DMAP, CH_2Cl_2, 98%). The equatorial C3-OTBDMS protecting group was selectively removed in the presence of the axial C1-OTBDMS to give **11** by using one equivalent of TBAF in THF at room temperature (74%). The selectivity of the desilylation reaction has been observed before[13c]. The C3 alcohol **11** was converted to the corresponding mesylate **12**, the C1-OTBDMS group was removed using TBAF to give the alcohol **13** (96%), which was oxidized using PDC in CH_2Cl_2. This oxidation was accompanied by simultaneous elimination of the C3-OMs group to afford directly the desired enone **15** (68%). Stereoselective reduction of enone **15** using $NaBH_4$ in the presence of $CeCl_3.7H_2O$ in MeOH gave enol **6** (75%).

A Mitsunobu reaction was then applied for introduction of the base moiety (Figure 6). Upon reaction

of **6** with adenine in the presence of DEAD and PPh_3 in dioxane, the desired adenine derivative **16a** was isolated in 40% yield, together with 15% of N7-isomer **16b** (Figure 6). Finally, removal of the benzoyl protecting groups using K_2CO_3 in MeOH gave the (L)-adenine cyclohexene nucleoside **7** in 72% yield. The corresponding (L)-guanine nucleoside **8** was synthesized in an analogous way. The enol **6** was treated with 2-amino-6-chloropurine under the same reaction condition as described above for **9**, and the obtained 6-chloropurine **17** was converted to the guanine derivative **18** using TFA-H_2O 3:1 (58% yield from **6**). Final deprotection was carried out by heating **18** in a saturated solution of NH_3 in MeOH in a sealed vessel for 2 days and reversed-phase HPLC purification gave pure (L)-guanine cyclohexene nucleoside **8** in 73% yield.

Antiviral activity

The anti-herpesvirus activity of D-cyclohexene G and L-cyclohexene G and the respective adenine analogues was determined in human embryonic skin muscle fibroblast (E_6SM: HSV-1, HSV-2) and in human embryonic lung (HEL) cells [varicella-zoster virus (VZV), cytomegalovirus (CMV)] (Table I). The source of the viruses and the methodology used to monitor antiviral activity have been previously described (De Clercq, E., Descamps, J., Verhelst, G., Walker, R.T., Jones, A.S., Torrence, P.F., Shugar, D. Comparative efficacy of antiherpes drugs against different strains of herpes simplex virus. J.Infect. Dis. 1980, **141**, 563-574; De Clercq, E., Hóly, A., Rosenberg, I., Sakuma, T., Balzarini, J., Maudgal, P.C. A novel selective broad-spectrum anti-DNA virus agent. Nature, 1986, **323**, 464-467). The antiviral activity was compared with the activity of known and approved antiviral drugs from which two with a purine base moiety (acyclovir, ganciclovir) and two with a pyrimidine base moiety (brivudine, cidofovir).

D-cyclohexene G as well as L-cyclohexene G did

not show toxicity in four different cell lines (HeLa, Vero, E_6SM, HEL) (Table II), pointing to their selective antiviral mode of action, as reflected by the high selectivity index of the compounds (Table I). A salient feature is that the activity spectrum of both enantiomers is remarkably similar. Both compounds display the same activity against HSV-1 and HSV-2. Against VZV and CMV the potency of L-cyclohexene G is about 2-fold lower than that of D-cyclohexene G. Against HSV-1, the cyclohexene G nucleosides are as active as acyclovir and brivudin. Against HSV-2, their activity is very similar to that of acyclovir. The cyclohexene G nucleosides retain activity against the TK^- strains of HSV-1 and VZV, although the activity is reduced as compared to the activity against the wild type. The activity of D-cyclohexene G against TK^+ and TK^- VZV strains is higher than the respective activities of acyclovir and brivudin against these viruses. D-cyclohexene G has the same activity against CMV as ganciclovir. In conclusion the activity spectrum of the cyclohexene nucleosides of the present invention is very similar to that of the known antiviral compounds possesing a guanine base moiety (acyclovir, ganciclovir). Both the D- and the L-enantiomers of cyclohexene G are antivirally active. The high selectivity indexes observed for D- and L-cyclohexene G indicates the utility of these compounds against herpesvirus infections.

D-cyclohexene G as well as L-cyclohexene G exhibited potent and selective anti-herpes virus (HSV1, HSV2, VZV, CMV) activity. Their activity spectrum is comparable to that of the known antiviral drugs acyclovir and ganciclovir. D- and L-cyclohexene G represent a very potent antiviral nucleosides containing a six-membered carbohydrate mimic. In contrast to the nucleosides with a cyclohexane, pyranose or hexitol ring, the cyclohexene nucleosides have a very flexible conformation. The inventors theorize that this flexibility may be an important structural determinant for their potent antiviral activity.

Experimental (1)

General Methods

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Philips PU 8740 UV/vis spectrophotometer. ^{1}H NMR and ^{13}C NMR were determined with a 200 MHz Varian Gemini apparatus with tetramethylsilane as internal standard for the ^{1}H NMR spectra and DMSO-d_6 (39.6 ppm) or $CDCl_3$ (76.9 ppm) for the ^{13}C NMR spectra (s = singlet, d = doublet, dd = double doublet, t = triplet, br s = broad singlet, br d = broad doublet, m = multiplet). Liquid secondary ion mass spectra (LSIMS) with Cs^+ as primary ion beam were recorded on a Kratos Concept IH (Kratos, Manchester, U.K.) mass spectrometer equipped with a MASPEC2 data system (Mass Spectrometry Services Ltd., Manchester, U.K.). Samples were directly dissolved in glycerol (gly)/thioglycerol (thgly)/*m*-nitrobenzyl alcohol (nba) and the secondary ions accelerated at 7kV. Scans were performed at 10 s/decade from *m/z* 1000 down to *m/z* 50. Precoated Machery-Nagel Alugram SIL G/UV_{254} plates were used for TLC (in solvent systems: A CH_2Cl_2-MeOH 98:2, B CH_2Cl_2-MeOH 9:1, C CH_2Cl_2-EtOAc 4:1); the spots were examined with UV light and sulfuric acid/anisaldehyde spray. Elemental analyses were done at the University of Konstanz, Germany.

9-[(1*S*,4*R*,5*S*)-5-(tert-butyldimethylsilyloxy)-4-(tert-butyldimethylsilyloxymethyl)-2-cyclohexenyl]-2-amino-6-chloropurine (9)

To a mixture of **3** (130 mg, 0.35 mmol), 2-amino-6-chloropurine (119 mg, 0.70 mmol) and PPh_3 (184 mg, 0.70 mmol) in dry dioxane (7 mL) under N_2 at room temperature was added a solution of DEAD (110 μL, 0.70 mmol) in dry dioxane (3 mL) over a period of 1.5 hr. The reaction mixture was stirred at room temperature for two days and concentrated. The residue was chromatographed on silica

gel (CH_2Cl_2-MeOH 50:1, then 20:1) to yield crude **9** (170 mg) as a yellow foam: ^1H NMR ($CDCl_3$) δ -0.10 (s, 3H), -0.04 (s, 3H), 0.07 (s, 6H), 0.82 (s, 9H), 0.90 (s, 9H), 2.04 (t, 2H, *J* = 5.6 Hz), 2.27 (m, 1H), 3.66 (dd, 1H, *J* = 9.9, 55.1 Hz), 3.77 (dd, 1H, *J* = 9.9, 4.4 Hz), 3.98 (m, 1H), 5.21 (m, 1H), 5.43 (s, 2H, NH_2), 5.79 (dm, 1H, *J* = 9.9 Hz), 6.00 (dm, 1H, *J* = 9.9 Hz), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -5.6 (q), -5.5 (q), -5.1 (q), -4.8 (q), 17.8 (s), 18.2 (s), 25.6 (q), 25.8 (q), 36.0 (t), 46.9 (d), 1049.2 (d), 62.9 (t), 64.6 (d), 124.4 (d), 125.4 (s), 134.4 (d), 141.3 (d), 151.1 (s), 153.3 (s), 159.1 (s);

9-[(1*S*,4*R*,5*S*)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine (5)

Crude **9** (170 mg) was treated with TFA-H_2O (3:1, 10 mL) at room temperature for two days. The reaction mixture was concentrated and co-evaporated with toluene (2x). The residue was chromatographed on silica gel (CH_2Cl_2-MeOH 10:1, then 1:1) to afford **5** (45 mg, 46% overall yield starting from **3**): Mp >230 °C; UV λ_{max} (MeOH) = 253 nm, ^1H NMR (CD_3OD) δ 1.94-2.27 (m, 3H), 3.77 (d, 2H, *J* = 4.7 Hz), 3.85 (m, 1H), 5.17 (m, 1H), 5.88 (dm, 1H, *J* = 10.2 Hz), 6.09 (dm, 1H, *J* = 10.2 Hz), 7.73 (s, 1H); ^{13}C NMR (CD_3OD) δ 37.1 (t), 47.7 (d), 50.6 (d), 63.1 (t), 64.8 (d), 125.8 (d), 135.4 (d), 138.5 (d); LISMS (THGLY/NBA) 278 $(M+H)^+$; HRMS calcd for $C_{12}H_{16}N_5O_3$ $(M+H)^+$ 278.1253, found 278.1270; Anal. Calcd for $C_{12}H_{15}N_5O_3.0.77H_2O$: C 49.49, H 5.73, N 24.05; Found: C 49.45, H 5.55, N 24.22.

(1*S*,2*S*,3*R*,5*R*)-3-Benzoyl-2-benzoylmethyl-1,5-di(*tert*-butyldimethylsilyloxy)-cyclohexane (10)

To a solution of **2b** (2.2 g, 5.64 mmol) in dry dichloromethane (20 mL) at 0 °C under N_2 was added DMAP (3.44 g, 28.2 mmol, 5 eq) and Bz_2O (3.83 g, 16.92 mmol, 3 eq) sequentially and in portions. After stirring at 0 °C for 2 hr, the reaction was quenched with ice. The

reaction mixture was poured into CH_2Cl_2 (250 ml) and washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was chromatographed on silica gel (*n*-hexane-EtOAc 10:1) to yield **10** (3.3 g, 98%) as a light yellow oil.

^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.13 (s, 3H), 0.17 (s, 3H), 0.89 (s, 9H), 1.01 (s, 9H), 1.58 (m, 2H), 2.09 (m, 2H), 2.37 (m, 1H), 4.29 (br-s, 1H), 4.40 (td, 1H, J = 10.3, 4.0 Hz), 4.49 (dd, 1H, J = 11.4, 2.0 Hz), 4.61 (dd, 1H, J = 11.4, 2.2 Hz), 5.66 (td, 1H, J = 11.0, 4.6 Hz), 7.37 - 7.44 (m, 4H), 7.49 - 7.59 (m, 2H), 8.02 (m, 4H);

^{13}C NMR ($CDCl_3$) δ -5.3 (q), -5.2 (q), -5.1 (q), -4.5 (q), 17.8 (s), 25.6 (q), 25.7 (q), 38.2 (t), 42.4 (t), 49.5 (d), 60.0 (t), 65.2 (d), 66.4 (d), 68.5 (d), 128.3 (d), 129.6 (d), 130.3 (s), 130.4 (s), 132.8 (d), 165.6 (s), 166.5 (s);

(1*S*,2*S*,3*R*,5*S*)-3-Benzoyl-2-benzoylmethyl-5-(*tert*-butyldimethylsilyloxy)-cyclohexanol (11)

A solution of TBAF 1M in THF (5.38 ml, 5.38 mmol) was added slowly to a solution of **10** (3.23 g, 5.38 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hr and further at room temperature for 3 hr. Ice was added and the reaction mixture was poured into EtOAc (300 ml) which was washed with NH_4Cl solution, water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified on silica gel (*n*-hexane-EtOAc 5:1 then 1:1) to yield **11** (1.93 g, 74%) as a white foam.

^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.09 (s, 3H), 0.81 (s, 9H), 1.50 - 1.63 (m, 2H), 1.96 (m, 1H), 2.13 (m, 1H), 2.32 (m, 1H), 3.24 (d, 1H, J = 4.8 Hz, -OH), 4.04 (m, 1H), 4.25 (m, 1H), 4.33 (dd, 1H, J = 11.4, 2.2 Hz), 5.04 (dd, 1H, J = 11.4, 2.2 Hz), 5.60 (td, 1H, J = 11.0, 4.5 Hz), 7.36 - 7.60 (m, 6H), 8.06 (m, 4H);

^{13}C NMR ($CDCl_3$) δ -5.2 (q), 17.6 (s), 25.4 (q), 38.2 (t),

40.8 (t), 50.4 (d), 59.8 (t), 64.1 (d), 66.1 (d), 68.4 (d), 128.4 (d), 129.6 (d), 129.8 (d), 130.4 (s), 133.0 (d), 133.2 (d), 165.6 (s), 167.6 (s);

LISMS (THGLY/TFA): 485 $(M+H)^+$; HRMS calcd for $C_{27}H_{37}O_6Si$ $(M+H)^+$ 485.2359, found 485.2376.

(1*S*,2*S*,3*R*,5*S*)-3-Benzoyl-2-benzoylmethyl-5-(*tert*-butyldimethylsilyloxy)-1-methanesulfonyloxy-cyclohexane (12)

To a solution of **11** (1.90 g, 3.92 mmol) in dry dichloromethane (20 mL) at 0 °C under N_2 was added slowly triethylamine (2.71 ml, 19.6 mmol, 5 eq) and MsCl (456 µl, 5.89 mmol, 1.5 eq) sequentially. After stirring at 0 °C for 1 hr, the reaction was quenched with ice. The reaction mixture was poured into CH_2Cl_2 (250 ml) and washed with a saturated NH_4Cl solution, water and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (*n*-hexane-EtOAc 1:1) to afford **12** (2.17 g, 98%) as a white foam.

^1H NMR ($CDCl_3$) δ 0.13 (s, 3H), 0.15 (s, 3H), 0.96 (s, 9H), 1.62 (td, 1H, *J* = 12.0, 2.0 Hz), 1.85 (td, 1H, *J* = 12.0, 2.0 Hz), 2.26 - 2.58 (m, 3H), 2.98 (s, 3H), 4.34 (m, 1H), 4.50 (dd, 1H, *J* = 11.4, 2.0 Hz), 4.60 (dd, 1H, *J* = 11.4, 2.0 Hz), 5.28 (td, 1H, *J* = 11.1, 4.8 Hz), 5.69 (td, 1H, *J* = 11.0, 4.8 Hz), 7.42 (m, 4H), 7.57 (m, 2H), 8.03 (m, 4H);

^{13}C NMR ($CDCl_3$) δ -5.3 (q), -5.2 (q), 17.8 (s), 25.5 (q), 37.8 (t), 38.1 (q), 39.9 (t), 46.7 (d), 58.9 (t), 65.9 (d), 67.8 (d), 75.9 (d), 128.5 (d), 129.6 (d), 129.9 (s), 133.1 (d), 165.4 (s), 166.3 (s);

LISMS (THGLY/GLY): 563 $(M+H)^+$; HRMS calcd for $C_{28}H_{39}O_8SSi$ $(M+H)^+$563.2135, found 563.2188.

(1*R*,3*S*,4*S*,5*R*)-5-Benzoyl-4-benzoylmethyl-3-methanesulfonyloxy-cyclohexanol (13)

To a solution of **12** (2.15 g, 3.82 mmol) in THF (50 mL) at room temperature was added slowly a 1 M

solution of TBAF (7.64 ml, 7.64 mmol, 2 eq) in THF. The reaction was stirred at room temperature for 2.5 hr and quenched with ice. After standard work-up and purification on silica gel (*n*-hexane-EtOAc 1:1), **13** (1.555g, 86%) was obtained as a white foam.

^{1}H NMR ($CDCl_3$) δ 1.71 (td, 1H, *J* = 12.1, 2.2 Hz), 1.90 (td, 1H, *J* = 12.2, 2.3 Hz), 2.29 - 2.65 (m, 4H), 3.00 (s, 3H), 4.41 (m, 1H), 4.52 (dd, 1H, *J* = 11.7, 2.8 Hz), 4.61 (dd, 1H, *J* = 11.7, 2.8 Hz), 5.27 (td, 1H, *J* = 10.6, 4.8 Hz), 5.65 (td, 1H, *J* = 10.6, 4.7 Hz), 7.42 (m, 4H), 7.55 (m, 4H), 8.02 (m, 4H);

^{13}C NMR ($CDCl_3$) δ 37.3 (t), 38.2 (q), 39.0 (t), 46.8 (d), 59.3 (t), 65.1 (d), 67.9 (d), 75.8 (d), 128.5 (d), 129.7 (d), 133.2 (d), 133.3 (d), 165.6 (s), 166.4 (s);

LISMS (THGLY/TFA): 449 $(M+H)^+$; HRMS calcd for $C_{22}H_{25}O_8S$ $(M+H)^+$ 449.1270, found 449.1244.

(4*S*,5*R*)-5-Benzoyl-4-benzoylmethyl-cyclohex-2-en-1-one (15)

A mixture of **13** (500 mg, 1.12 mmol) and PDC (2.1 g, 5.60 mmol, 5 eq) in dry CH_2Cl_2 (30 mL) was stirred vigorously at room temperature for 24 h. The reaction mixture was filtered through Celite® and washed with CH_2Cl_2. The filtrate was concentrated and the residue was chromatoghraphed on silica gel (*n*-hexane-EtOAc 2:1, then 1:2) to yield starting material **13** (100 mg, 20 %) and enone **15** (267 mg, 68%) as a light yellow oil.

^{1}H NMR ($CDCl_3$) δ 2.73 (dd, 1H, *J* = 16.5, 8.8 Hz), 3.10 (dd, 1H, *J* = 16.5, 4.4 Hz), 3.27 (m, 1H), 4.50 (dd, 1H, *J* = 11.3, 4.7 Hz), 4.66 (dd, 1H, *J* = 11.3, 5.5 Hz), 5.66 (ddd, 1H, *J* = 8.8, 7.3, 4.4 Hz), 6.26 (dd, 1H, *J* = 10.2, 2.2 Hz), 6.96 (dd, 1H, *J* = 10.2, 3.3 Hz), 7.40 - 7.63 (m, 6H), 8.01 (m, 4H);

^{13}C NMR ($CDCl_3$) δ 41.3 (d), 42.1 (t), 63.2 (t), 70.0 (d), 128.6 (d), 129.5 (2s), 129.7 (d), 129.8 (d), 131.4 (d), 133.5 (d), 146.5 (d), 165.5 (s), 166.4 (s), 195.8 (s);

(1S,4*S*,5*R*)-5-Benzoyl-4-benzoylmethyl-cyclohex-2-en-1-ol (6)

To a solution of **15** (267 mg, 0.76 mmol) in MeOH (10 mL) at room temperature under N_2 was added $CeCl_3.7H_2O$ (426 mg, 1.14 mmol, 1.5 eq). The mixture was stirred for 0.5 h and a clear solution was obtained. $NaBH_4$ (35 mg, 0.91 mmol, 1.2 eq) was added in portions and H_2 evolved. The reaction mixture was stirred for 1 h and quenched with ice. The mixture was stirred for 15 min and concentrated. The residue was distributed into EtOAc, washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (*n*-hexane-EtOAc 10:1) to give **6** (200 mg, 75%) as a light yellow oil.

^1H NMR ($CDCl_3$) δ 1.77 (d, 1H, J = 7.2 Hz), 1.93 (ddd, 1H, J = 12.1, 10.2, 8.0 Hz), 2.54 (ddd, 1H, J = 12.1, 5.8, 3.3 Hz), 3.00 (m, 1H), 4.32 (dd, 1H, J = 11.4, 5.5 Hz), 4.44 (dd, 1H, J = 11.4, 5.5 Hz), 4.50 (m, 1H), 5.35 (ddd, 1H, J = 10.2, 7.3, 2.9 Hz), 5.78 (dt, 1H, J = 10.2, 1.8 Hz), 5.97 (dt, 1H, J = 10.2, 2.5 Hz), 7.34 - 7.60 (m, 6H), 8.00 (m, 4H);

^{13}C NMR ($CDCl_3$) δ 36.6 (t), 40.9 (d), 46.6 (t), 65.8 (d), 69.9 (d), 126.6 (d), 128.4 (d), 128.5 (d), 129.7 (d), 129.8 (s), 130.9 (s), 132.7 (d), 133.1 (d), 133.2 (d), 166.0 (s), 166.5 (s);

LISMS (THGLY/TFA): 353 $(M+H)^+$; HRMS calcd for $C_{21}H_{21}O_5$ $(M+H)^+$ 353.1389, found 353.1440.

9-[(1*R*,4*S*,5*R*)-5-Benzoyl-4-benzoylmethyl-2-cyclohexenyl]adenine (16a)

To a mixture of **6** (65 mg, 0.18 mmol), adenine (48 mg, 0.36 mmol, 2 eq) and PPh_3 (94 mg, 0.36 mmol, 2 eq) in dry dioxane (4 mL) under N_2 at room temperature was added a solution of DEAD (56 µL, 0.36 mmol, 2 eq) in dry dioxane (3 mL) over a period of 1 hr. The reaction mixture was stirred at room temperature overnight and concentrated. The residue was chromatographed on silica

gel (CH_2Cl_2-MeOH 50:1, 20:1, 10:1) to yield **16a** (33 mg, 40%) as a white solid.

UV λ_{max} (MeOH): 231 and 263 nm.

^1H NMR ($CDCl_3$) δ 2.48 (ddd, 1H, J = 13.6, 8.3, 5.8 Hz), 2.57 (ddd, 1H, J = 13.6, 6.0, 3.2 Hz), 4.50 (dd, 1H, J = 10.4, 5.0 Hz), 4.63 (dd, 1H, J = 10.4, 6.1 Hz), 5.53 (m, 2H), 5.92 (s, 2H), 6.09 (dm, 1H, J = 10.0 Hz), 6.17 (dm, 1H, J = 10.0 Hz), 7.41 (m, 4H), 7.57 (m, 2H), 7.86 (s, 1H), 8.04 (m, 4H), 8.35 (s, 1H);

^{13}C NMR ($CDCl_3$) δ 32.4 (t), 40.6 (d), 48.7 (d), 64.3 (t), 68.2 (d), 120.1 (s), 126.8 (d), 128.5 (d), 128.6 (d), 129.6 (d), 129.7 (d), 131.0 (d), 133.4 (d), 138.8 (d), 149.8 (s), 153.1 (d), 155.8 (s), 165.8 (s), 166.5 (s);

LISMS (THGLY/NBA): 470 $(M+H)^+$; HRMS calcd for $C_{26}H_{24}N_5O_4$ $(M+H)^+$ 470.1828, found 470.1845.

9-[(1*R*,4*S*,5*R*)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine (7)

Compound **16a** (33 mg, 0.07 mmol) was treated with anhydrous K_2CO_3 (100 mg) in MeOH (3 mL) at room temperature for 3 hr. Small portion of silica gel was added to the reaction mixture and the solvent was evaporated. The residue was chromatographed on silica gel (CH_2Cl_2-MeOH 10:1, 1:1) to give 7 (14 mg, 77%).

^1H NMR (CD_3OD) δ 2.02 - 2.32 (m, 3H), 3.79 - 3.90 (m, 3H), 5.35 (m, 1H), 5.93 (dm, 1H, J = 9.9 Hz), 6.15 (dm, 1H, J = 9.9 Hz), 8.09 (s, 1H), 8.21 (s, 1H);

^{13}C NMR (CD_3OD) δ 37.2 (t), 47.7 (d), 51.1 (d), 63.0 (t), 64.7 (d), 120.6 (s), 125.4 (d), 136.0 (d), 141.6 (d), 150.3 (s), 153.8 (d), 157.5 (s);

LISMS (THGLY/TFA): 262 $(M+H)^+$; HRMS calcd for $C_{12}H_{16}N_5O_2$ $(M+H)^+$ 262.1304, found 262.1323.

9-[(1*R*,4*S*,5*R*)-5-Benzoyl-4-benzoylmethyl-2-cyclohexenyl]guanine (18)

Compound 6 (160 mg, 0.45 mmol) was treated with 2-amino-6-chloropurine (153 mg, 0.90 mmol, 2 eq) in the

presence of PPh_3 (235 mg, 0.90 mmol, 2 eq) and DEAD (140 µl, 0.90 mmol, 2 eq) in dry dioxane (12 mL) at room temperature overnight. After concentration and purification on silica gel (CH_2Cl_2-EtOAc 1:1), crude **17** (500 mg) was obtained, which was treated with CF_3COOH/H_2O (3:1, 12 mL) at room temperature for 2 days. The reaction mixture was concentrated and coevaporated with toluene. The residue was purified on silica gel (CH_2Cl_2-MeOH 20:1) to yield **18** (126 mg, 58% over two steps) as a white solid.

UV λ_{max} (MeOH): 251 and 256 nm.

^{1}H NMR (500 MHz, DMSO-d_6) δ 2.30 (ddd, 1H, J = 13.6, 8.3, 5.9 Hz), 2.42 (ddd, 1H, J = 13.6, 6.4, 3.2 Hz), 3.00 (m, 1H), 4.52 (m, 2H), 5.17 (m, 1H), 5.37 (m, 1H), 6.03 (dm, 1H, J = 10.2 Hz), 6.11 (dm, 1H, J = 10.2 Hz), 6.45 (s, 2H), 7.51 (m, 4H), 7.66 (m, 2H), 7.69 (s, 1H), 7.95 (m, 4H), 10.61 (s, 1H);

^{13}C NMR (DMSO-d_6) δ 31.4 (t), 40.0 (d, overlapped with DMSO-d_6 peak), 47.9 (d), 64.4 (t), 68.5 (d), 116.9 (s), 127.0 (d), 128.9 (d), 129.3 (d), 129.4 (d), 130.2 (d), 133.6 (d), 135.7 (d), 150.9 (s), 153.8 (s), 156.9 (s), 165.3 (s), 165.8 (s);

LISMS (THGLY/GLY): 486 $(M+H)^+$; HRMS calcd for $C_{26}H_{24}N_5O_5$ $(M+H)^+$ 486.1777, found 486.1816;

UV (MeOH): 231, 256.

9-[(1*R*,4*S*,5*R*)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine (8)

A mixture of **18** (85 mg) in an ammonium MeOH solution (75 mL) was sealed and heated at 80 °C for 2 days. After cooling to room temperature, the mixture was concentrated and the residue was purified by reverse HPLC (4% CH_3CN in water) to afford **8** (36 mg, 75%) as a white powder.

Mp: 255 °C (decomp.)

UV λ_{max} (MeOH) = 254 nm.

^{1}H NMR (500 HMz, DMSO-d_6) δ 1.85 (m, 1H), 1.98 (m, 1H),

2.11 (m, 1H), 3.54 (dd, 1H, J = 10.3, 5.5 Hz), 3.60 (dd, 1H, J = 10.3, 4.8 Hz), 3.70 (m, 1H), 4.68 (br-s, 1H, -OH), 4.75 (br-s, 1H, -OH), 4.99 (m, 1H), 5.77 (dm, 1H, *J* = 9.8 Hz), 5.97 (dm, 1H, *J* = 9.8 Hz), 6.57 (s, 2H, $-NH_2$), 57.50 (s, 1H), 10.8 (br-s, 1H, -NH);

^{13}C NMR (125 MHz, DMSO-d_6) δ 35.9 (t), 46.4 (d), 48.2 (d), 61.5 (t), 62.7 (d), 116.9 (s), 124.8 (d), 133.7 (d), 135.6 (d), 150.8 (s), 154.1 (s), 157.6 (s);

LISMS (THGLY/NBA) 278 $(M+H)^+$; HRMS calcd for $C_{12}H_{16}N_5O_3$ $(M+H)^+$ 278.1253, found 278.1247; Anal. Calcd for $C_{12}H_{15}N_5O_3.1.5H_2O$: C 47.35, H 5.96, N 23.03; Found: C 47.46, H 5.64, N 22.87.

As detailed above, the inventors have developed an enantioselective approach to the synthesis of six-membered carbocyclic nucleosides of type **2b** (R = OH) starting from (*R*)-(-)-carvone (**4**, Figure 7, corresponding substantially with Figure 1). A key step involving hydroboration of the exo double bond of cyclohexene **6b** to afford hydroxymethyl substituted **7b** with the correct stereochemistry at C4. Precursor **6a** provided an ideal starting material for the synthesis of **3** as it had (1) a protected hydroxyl group at C3, (2) a protected hydroxyl substituent at C1, which at a final stage can be used to introduce a base moiety with retention of the configuration using Pd-chemistry, and (3) a free hydroxyl group at C5, which could be used to introduce the double bond.

The most straightforward approach seemed to introduce the C5-C6 double bond *via* conversion of the OH at C5 into a suitable leaving group, followed by a regioselective elimination. The latter might be achieved *via* a E_2-type elimination reaction by treatment with base, which requires a neighbouring hydrogen *trans* to the leaving group, only available on C6. In order to explore this strategy, alcohol **6a** was converted into diol **7a** *via* hydroboration using 9-BBN in THF. The reaction gave **7a** as the major isomer, together with a small amount of epimer

8a. The β-stereochemistry at C4 was easily established by NMR spectrometry. Selective protection of the primary hydroxyl group of **7a** (TBDMSCl, imidazole, DMF) gave **9** (Figure 8) and the leaving group was introduced (MsCl, Et_3N, dichloromethane) to give **10**. However, upon treatment of mesylate **10** with DBU in toluene, cyclohexene **11** was not formed. More vigorous reaction conditions (KOH, H_2O-THF),[5] likewise, failed to yield the unsaturated compound **11**. Direct elimination of the 5-OH of **9** under Mitsunobu conditions (DEAD, PPh_3, THF)[6] was also unsuccessful. **9** was converted into the β-iodide **12** (I_2, PPh_3, imidazole, toluene), with inversion of the stereochemistry at C5, followed by treatment with DBU in refluxing toluene. This reaction resulted in an inseparable mixture (yield 68%) of cyclohexenes **11** and **13** in a 1:2.3 ratio, respectively, in favour of the undesired regioisomer.

The inventors also investigated a different synthetic strategy, i.e. the construction of an allylic acetate of type **A** or **B** (Figure 1) as intermediate for the Pd coupling reaction to introduce the base moiety.

Diol **14** (Figure 9) was protected as cyclic acetal **15** (2,2-dimethoxypropane, PPTS, acetone-THF), the Bn group was removed (10% Pd on carbon, $HCOONH_4$, MeOH, reflux) to give alcohol **16**, and oxidation of the C5-OH (PDC, dichloromethane) provided ketone **17**. Cleavage of the TBDMS ether using tetrabutylammonium fluoride (TBAF) in THF led mainly to diol **18**. However, under neutral reaction conditions (KF, 18-crown-6, THF) the desired enone **19** was isolated in 62% yield; the β-hydroxy ketone intermediate **20** could not be detected. The critical reduction of enone **19** to the corresponding allylic alcohol **22** with β-oriented OH at C5 proved to be problematic, leading almost exclusively to the α-isomer **21** under the applied reaction conditions ($NaBH_4$, $CeCl_3.7H_2O$, MeOH and 9-BBN, THF). In an attempt to invert the stereochemistry at C5 of α-alcohol **21**, the latter was

subjected to a Mitsunobu type reaction (DEAD, PPh_3, AcOH), but the desired β-acetate **23** was not formed. However, compound **21** might be used to synthesize the α-analogue of the aforementioned cyclohexene nucleoside, interesting for as well conformational analysis as for determination of antiviral activity.

The intended Pd coupling reaction was investigated on the α-acetate **24**, easily prepared from **21** (Ac_2O, DMAP, dichloromethane). When **24** was treated with the anion (NaH) of adenine in the presence of tetrakis(triphenylphosphine)palladium(0) in DMF-THF, only **24** was recovered and no trace of the 1α-adenine **25** could be detected. Reasoning that this failure might be due to the rigidity of the cyclic acetal present, **24** was treated with PPTS in MeOH to give diol **26**, which was then converted into the corresponding dibenzoate **27** (Bz_2O, DMAP, dichloromethane). However, upon subjection of **27** to the same reaction conditions for coupling as applied above to **24**, the expected 1α-adenine product **28** could not be isolated.

The above failure having exhausted the possibilities of the Pd coupling strategy, the most reliable alternative (for the introduction of the base moiety seemed) a Mitsunobu reaction was utilized, i.e. by substitution with inversion of the configuration of an α-oriented hydroxyl group at C1. Therefore the inventors had to synthesize an appropriately protected precursor **7c**. Epoxide **5b** (Figure 7, R_1 = Bn) was converted into **6c** under the reported conditions (LiTMP and Et_2AlCl in benzene-toluene 1:1) in 79% yield. Hydroboration of **6c** with 9-BBN in THF afforded **7c** as major isomer (74%), together with its epimer **8c** (20%). Similar to configurational assignment of **7a** and **7b**, the β-stereochemistry at C4 of **7c** was established by ^1H-NMR. The primary hydroxyl group of **7c** was selectively protected using 1.2 equivalents of TBDMSCl and imidazole in DMF t_e

2ve **29** (70%, Figure 10), followed by conversion of the free alcohol at C5 into the corresponding mesylate **30** by treatment with MsCl and Et_3N in dichloromethane. Hydrogenolytic cleavage of the benzyl ether at C1 using 520% $Pd(OH)_2$ on carbon in the presence of cyclohexene in MeOH gave **31** in low yield (21%), which could be improved to 76% by the use of 10% Pd on carbon and $HCOONH_4$ in refluxing MeOH. Oxidation of alcohol **31** using PDC in dichloromethane gave a mixture of ketone **32** and enone **33** 10in a combined yield of 39%. However, using MnO_2 in dichloromethane, an incomplete but clean reaction took place. The ketone **32** was not isolated and enone **33** was obtained in 48% yield and recovered **31** (47%) could be recycled. Finally, enone **33** was reduced using $NaBH_4$ in the 15presence of $CeCl_3.7H_2O$ in MeOH and gave the desired α-alcohol **34** as a single isomer in almost quantitative yield. The stereochemistry of **34** was confirmed by ^1H NMR spectral data. In $CDCl_3$ conformation **A** (Figure 2), with the three substituents in a pseudoaxial position, 20predominates due to intramolecular hydrogen bonding between the C1-OH and C3-OTBDMS groups, while in DMSO-d_6 it adopts conformation **B**. This reflects the much lower axial-equatorial energy differences in cyclohexenes as compared to the corresponding cyclohexanes.

25 With intermediate **34** in hand, the base moiety (adenine) was introduced under Mitsunobu reaction conditions. Upon treatment of **34** with adenine in the presence of DEAD and PPh_3 in dioxane at room temperature for 1 day, **35a** was isolated in 66% yield, together with 3017% of its N_7-isomer **35b** (Figure 11). Complete deprotection of **35a** using TBAF in THF at room temperature afforded the desired cyclohexene carbocyclic nucleoside **36** in almost quantitative yield. However, the compound was contaminated with tetrabutylammonium salts which 35could not be removed by standard chromatographic techniques. Recently Parlow et al. described a work-up procedure to remove tetrabutylammonium salts by the

direct addition to the reaction mixture of mixed ion-exchange resins Amberlite® 15 and Amberlite® 15 in the Ca^{2+} form. Applied to the above TBAF reaction a complex mixture was obtained, giving **36** in low yield. In order to avoid the use of TBAF, Megron's method (Megron, G.; Vasquezy, F.; Galderon, G.; Cruz, R.; Gavino, R.; Islas, G. Synth. Commun. 1998, 26(16), 3021-3027) was used: compound **35a** was treated with potassium *tert*-butoxide in DMF at room temperature. However, only a complex, reaction mixture was obtained, due to the strong basic character of the reaction conditions. Finally **35a** was treated with a 3:1 mixture of TFA and H_2O at room temperature, which smoothly gave **36** in 54% overall yield starting from **34**. According to our experience, this is the best procedure to cleave TBDMS ethers of this type of compound. Finally, **36** was purified by reversed-phase HPLC for analysis and determination of biological activity.

The above intermediate 36 (Figure 11) gave the inventors the opportunity to obtain as yet 2a (B = adenine) in enantiopure form via reduction of the double bond. Thus, 36 was hydrogenated using H2 under atmospheric pressure in the presence 10% Pd on carbon in MeOH at room temperature to afford D-2a in 75% yield. The spectral data of D-2a were superimposable with those of a DL mixture of 2a. The enantiomeric purity of D-2a was examined by HPLC on a chiral column. The separation of a DL mixture of 2a together with the HPLC profile of D-2a synthesized by the above approach is depicted in reference 3c. Its enantiomeric purity proved 99%, at the same time establishing the high enantiomeric purity of **36**.

The inventors have developed an enantioselective approach towards the synthesis of cyclohexene carbocyclic nucleosides starting from (*R*)-carvone **4**. The synthetic methodology makes use of a Mitsunobu reaction as the key step to introduce the heterocyclic base moiety. The reaction proved to be efficient as well as chemo- and stereoselective, while

the commonly applied palladium-mediated coupling strategy was unsuccessful. ^1H NMR and computation results show that in solution the synthesized adenine derivative **36** exists predominantly in a $^3H_2$ half-chair conformation with the adenine base orienting in a pseudoaxial position. The energy difference between $^3H_2$ and $^2H_3$ is, however, low. This compound may therefore be considered as a good mimic of a furanose nucleoside, showing two low energy conformations with a preference for the "3'-endo conformation". This is also the preferred conformation of a hexitol nucleoside, in the $^1C_4$ conformation. Moreover, the inventors theorize that the easy interconversion among both conformers might be a factor for antiviral activity.

Experimental (2)

(1*R*,3*S*,5*R*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-methylenecyclohexanol (6c)

A solution of 2,2,6,6-tetramethylpiperidine (TMP, 27.3 mL, 162 mmol) in dry benzene (80 mL) and dry toluene (80 mL) was cooled to 0 °C under N_2 and a solution of *n*-BuLi in hexane (1.6 M, 64.8 mL, 162 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 10 min and a solution of Et_2AlCl (1.8 M, 90 mL, 162 mmol) in toluene was slowly added over a period of 1 hr. The reaction was stirred for an additional 30 min. A solution of **5b** (14.1 g, 40.5 mmol) in benzene (30 mL) was added slowly. The reaction mixture was stirred at 0 °C for 3 h, then poured into an ice-cold NH_4Cl solution (300 mL). A 3 N HCl solution was added until a clear emulsion was obtained. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (*n*-hexane-EtOAc 10:1) to give **6c** (10.2 g, 71%) as a light-yellow oil: ^1H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.92

(s, 9H), 1.90 (m, 4H), 2.69 (d, 1H, J = 7.3 Hz, OH), 4.05 (m, 1H), 4.45 (m, 2H), 4.58 (s, 2H), 5.05 (s, 1H), 5.07 (s, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -5.1 (q), 18.0 (s), 25.7 (q), 40.7 (t), 40.9 (t), 70.4 (d and t, overlapped), 70.8 (d), 71.3 (d), 107.1 (t), 127.5 (d), 128.4 (d), 138.7 (s), 150.7 (s).

(1*R*,2*S*,3*S*,5*R*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-hydroxymethyl-cyclohexanol (7c) and its epimer 8c

To a solution of _0 (10.8 g, 31.03 mmol) in dry THF (80 mL) at 0 °C under N_2 was added slowly a solution of 9-BBN in THF (0.5 M, 155 mL, 77.58 mmol). The reaction mixture was slowly warmed up to rt overnight. The reaction was cooled to 0 °C and treated sequentially with EtOH (30 mL), a 2 N NaOH solution (60 mL) and a 35% H_2O_2 solution (60 mL) under stirring. The resulting mixture was stirred at rt for 24 h, then poured into a mixture of EtOAc (300 mL) and H_2O (300 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The crude product was separated on silica gel (*n*-hexane-EtOAc 5:1, then 1:1) to yield **7c** (8.4 g, 74%) and epimer **8c** (2.28 g, 20%) as a light-yellow oils.

7c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (2s, 6H), 0.91 (s, 9H), 1.52 (ddd, 1H, J = 13.1, 10.1, 2.8 Hz), 1.54 (ddd, 1H, J = 13.1, 10.1, 3.1 Hz), 1.69 (tdd, 1H, J = 10.0, 7.5, 4.1 Hz), 2.10 (dt, 1H, J = 13.1, 4.1 Hz), 2.16 (dt, 1H, J = 13.1, 4.1 Hz), 2.71 (s, 1H), 3.11 (s, 1H), 3.78 (dd, 1H, J = 10.1, 7.5 Hz), 3.85 (td, 1H, J = 10.0, 4.2 Hz), 3.86 (m, 1H), 3.97 (br-td, 1H, J = 10.1, 4.1 Hz), 4.04 (br-dd, 1H, J = 10.1, 4.1 Hz), 4.51 (s, 2H), 7.26-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -5.0 (q), -4.3 (q), 17.8 (s), 25.7 (q), 38.1 (t), 38.4 (t), 53.2 (d), 63.4 (t), 68.0 (d), 69.4 (d), 70.3 (t), 72.4 (d), 127.4 (d), 127.6 (d), 128.4 (d), 138.7 (s); LISMS (THGLY): 367 $(M+H)^+$; HRMS calcd for $C_{20}H_{35}O_4Si$ $(M+H)^+$ 367.2305, found 367.2341.

8c: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 1.40-1.87 (m, 3H), 2.25 (dm, 1H, *J* = 13.2 Hz), 2.48 (dm, 1H, *J* = 13.2 Hz), 3.69 - 4.20 (m, 6H), 4.33 (m, 1H), 4.53 (d, 1H, *J* = 11.7 Hz), 4.62 (d, 1H, *J* = 11.7 Hz), 57.33 (m, 5H), 8.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -5.6 (q), -5.0 (q), 21.9 (s), 25.5 (q), 39.2 (2t, overlapped), 45.9 (d), 61.3 (t), 69.0 (d), 69.4 (d), 70.4 (t), 70.8 (d), 127.6 (d), 127.7 (d), 128.4 (d), 138.6 (s); LISMS (THYLY): 367 $(M+H)^+$; HRMS calcd for $C_{20}H_{35}O_4Si$ $(M+H)^+$ 10367.2305, found 367.2335.

(1*R*,2*R*,3*S*,5*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldimethylsilyloxy methyl)cyclohexanol (29).

To a solution of **7c** (2.5 g, 6.83 mmol) in DMF 15(50 mL) at rt were added imidazole (930 mg, 13.66 mmol) and TBDMSCl (1.23 g, 8.2 mmol) in portions. The reaction was stirred at rt overnight and quenched with ice. The resulting mixture was evaporated to remove DMF and the residue was partitioned between EtOAc and H_2O. The layers 20were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (*n*-hexane-EtOAc 5:1) to yield **29** (2.28 g, 70%) as a light-yellow oil: ^{1}H 25NMR ($CDCl_3$) δ 0.05, 0.06, 0.09 (3s, 12H), 0.89, 0.91 (2s, 18H), 1.53 (m, 2H), 1.72 (qd, 1H, *J* = 9.5, 4.4 Hz), 2.11 (m, 2H), 3.67 (t, 1H, *J* = 9.5 Hz), 3.78 (td, 1H, *J* = 9.5, 4.4 Hz), 3.87 (m, 1H), 4.01 (m, 1H), 4.16 (dd, 1H, *J* = 9.5, 4.4 Hz), 4.46 (d, 1H, *J* = 15.2 Hz), 4.48 (d, 1H, *J* = 3015.2 Hz), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -5.7 (q), -5.1 (q), -4.3 (q), 17.8, 18.0 (2s), 25.7 (2q), 37.0 (t), 38.4 (t), 52.2 (d), 66.2 (t), 67.2 (d), 70.1 (t and d overlapped), 72.4 (d), 127.3 (d), 127.4 (d), 128.4 (d), 138.9 (s); LISMS (GLY): 481 $(M+H)^+$; HRMS cald for 35$C_{26}H_{49}O_4Si_2$ $(M+H)^+$ 481.3169, found 481.3199.

(1*R*,2*R*,3*S*,5*S*)-5-Benzyloxy-2-(*tert*-

butyldimethylsilyloxymethyl)-3-(*tert*-butyldimethylsilyoxy)-1-methanesulfonyloxy-cyclohexane (30)

To a solution of **29** (5.4 g, 11.25 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added triethylamine (7.8 mL, 556.25 mmol), followed by dropwise addition of MsCl (1.3 mL, 16.87 mmol). The reaction was stirred at 0 °C for 1h and treated with ice. The resulting mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with a diluted HCl solution, H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (*n*-hexane-EtOAc 5:1) to afford **30** (5.81 g, 92%) as a white solid: mp 100-101 °C; ^1H NMR ($CDCl_3$) δ 0.08 (2s, 12H), 0.89 (s, 9H), 0.90 (s, 9H), 1.43 (ddd, 1H, J = 13.9, 10.0, 2.8 Hz), 1.62 (tt, 1H, J = 10.2, 2.0 Hz), 1.71 (ddd, 1H, J = 12.8, 10.6, 2.2 Hz), 2.24 (br-d, 1H, J = 13.9 Hz), 2.69 (br-d, 1H, J = 12.8 Hz), 3.01 (s, 3H), 3.74 (dd, 1H, J = 9.9, 2.2 Hz), 3.89 (m, 1H), 3.91 (dd, 1H, J = 9.9, 1.8 Hz), 4.19 (td, 1H, J = 10.0, 4.7 Hz), 4.45 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz), 5.13 (td, 1H, J = 10.6, 4.8 Hz), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -5.6 (q), -5.3 (q), -4.6 (q), -3.7 (q), 17.9 (s), 25.8 (q), 35.5 (t), 38.5 (t), 38.8 (q), 51.8 (d), 56.9 (t), 65.1 (d), 70.1 (t), 72.0 (d), 77.5 (d), 127.4 (d), 128.4 (d), 138.5 (s); LISMS(GLY/NBA) 559 $(M+H)^+$; HRMS calcd for $C_{27}H_{51}O_6SSi_2$ $(M+H)^+$ 559.2945, found 559.2979; Anal. Calcd for $C_{27}H_{51}O_6SSi_2$: C 58.02, H 9.02; Found: C 57.96, H 8.82.

(1*S*,3*R*,4*R*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-*tert*-butyldimethylsilyloxy-3-methanesulfonyloxy-cyclohexanol (31)

A mixture of **30** (3.5 g, 6.27 mmol), Pd/C (10 %, 4.4 g) and $HCOONH_4$ (2.2 g) in MeOH (100 mL) was refluxed and 2 x 1.1 g of $HCOONH_4$ were added every 3 h interval. The reaction was refluxed until all the starting material was consumed (total 14 h). After cooling to rt, the

reaction mixture was filtered through Celite® and the residue was washed with CH_2Cl_2 (3x). The filtrate was concentrated to afford crude **31** (2,83 g, 97%) as a white solid, which was used as such for the next step: mp 135-137 °C; ^1H NMR ($CDCl_3$) δ 0.08, 0.09 (2s, 12H), 0.89 (s, 9H), 0.92 (s, 9H), 1.43 - 1.68 (m, 3H), 1.83 (ddd, 1H, *J* = 13.2, 10.6, 2.8 Hz), 2.07 (br-d, 1H, *J* = 13.2 Hz), 2.44 (br-d, 1H, *J* = 13.2 Hz), 3.02 (s, 3H), 3.72 (dd, 1H, *J* = 10.0, 2.4 Hz), 3.90 (dd, 1H, *J* = 10.0, 2.4 Hz), 4.19 (td, 1H, *J* = 10.6, 4.1 Hz), 4.26 (m, 1H), 5.14 (td, 1H, *J* = 10.6, 4.7 Hz); ^{13}C NMR ($CDCl_3$) δ -5.6 (q), -5.3 (q), -4.7 (q), -3.8 (q), 17.9 (s), 25.8 (q), 38.8 (q), 38.9 (t), 40.8 (t), 51.7 (d), 57.1 (t), 64.9 (d), 65.5 (d), 77.3 (d); LISMS (GLY/NBA) 469 $(M+H)^+$; HRMS calcd for $C_{20}H_{45}O_6SSi_2$ $(M+H)^+$ 469.2475, found 469.2453; Anal. Calcd for $C_{20}H_{45}O_6SSi_2$: C 51.24, H 9.46; Found: C 51.24, H 9.36.

(4*R*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-tert-butyldimethylsilyloxy-cyclohex-2-en-1-one (33)

A mixture of crude **31** (2.83 g, 6.27 mmol) and MnO_2 (13.6 g, 156.8 mmol) in dry CH_2Cl_2 (100 mL) was stirred vigorously at rt for 21 h. The reaction mixture was filtered through Celite® and washed with CH_2Cl_2. The filtrate was concentrated and the residue was chromatoghraphed on silica gel (*n*-hexane-EtOAc 5:1, then 1:2) to yield starting material **30** (1.56 g, 53 %) and enone **33** (920 mg, 40% over two steps) as a light-yellow oil (solid upon storing in the refrigerator): ^1H NMR ($CDCl_3$) δ 0.07 (s, 12H), 0.89 (s, 18H), 2.50 (m, 1H), 2.46 (dd, 1H, *J* = 16.1, 10.6 Hz), 2.72 (dd, 1H, *J* = 16.1, 4.8 Hz), 3.73 (dd, 1H, *J* = 9.9, 5.6 Hz), 3.85 (dd, 1H, *J* = 9.9, 4.4 Hz), 4.09 (ddd, 1H, *J* = 10.6, 8.1, 4.8 Hz), 6.06 (dd, 1H, *J* = 10.2, 2.6 Hz), 6.88 (dd, 1H, *J* = 10.2, 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ -5.6 (q), -5.5 (q), -5.1 (q), -4.4 (q), 17.8 (s), 18.2 (s), 25.6 (q), 25.8 (q), 47.1 (t), 48.0 (d), 61.8 (t), 68.0 (d), 130.2 (d), 150.6 (d), 199.0 (s); LISMS (THGLY/NBA) 371 $(M+H)^+$; HRMS calcd for

$C_{19}H_{39}O_3Si_2$ $(M+H)^+$ 371.2438, found 371.2432.

(1R,4*R*,5*S*)-5-(tert-Butyldimethylsilyloxy)-4-(tert-butyldimethylsilyloxymethyl)-cyclohex-2-en-1-ol (34)

To a solution of **33** (920 mg, 2.49 mmol) in MeOH (35 mL) at rt under N_2 was added $CeCl_3.7H_2O$ (1.39 g, 3.73 mmol). The mixture was stirred for 0.5 h and a clear solution was obtained. $NaBH_4$ (113 mg, 2.99 mmol) was added in portions and H_2 evolved. The reaction mixture was stirred for 1 h and quenched with H_2O. The mixture was stirred for 15 min and concentrated. The residue was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (*n*-hexane-EtOAc 10:1) to give **34** (844 mg, 91%) as a colourless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.94 (ddd, 1H, J = 13.7, 5.3, 3.9 Hz), 1.99 (ddd, 1H, J = 13.7, 4.5, 2.6 Hz), 2.36 (m, 1H), 2.94 (d, 1H, J = 9.8 Hz), 3.38 (dd, 1H, J = 10.1, 7.8 Hz), 3.56 (dd, 1H, J = 10.1, 5.0 Hz), 4.09 (pseudo sext, 1H, J = 9.8, 4.5, 4.0, 3.9 Hz), 4.20 (pseudo pent, 1H, J = 5.3, 3.4, 2.6 Hz), 5.61 (dd, 1H, J = 10.0, 3.9 Hz), 5.95 (ddd, 1H, J = 10.0, 4.0, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ -5.5 (q), -5.4 (q), -4.9 (q), -4.8 (q), 18.0 (s), 18.3 (s), 25.8 (q), 25.9 (q), 35.6 (t), 46.5 (d), 63.5 (t), 64.8 (d), 67.7 (d), 127.0 (d), 131.1 (d); LISMS (THGLY/NBA) 373 $(M+H)^+$; HRMS calcd for $C_{19}H_{40}O_3Si_2$ $(M+H)^+$ 373.2594, found 373.2626; Anal. Calcd for $C_{19}H_{40}O_3Si_2$: C 61.23, H 10.82; Found: C 61.34, H 10.83.

9-[(1*S*,4*R*,5*S*)-5-(tert-Butyldimethylsilyloxy)-4-(tert-butyldimethylsilyloxymethyl)-2-cyclohexenyl]adenine (35a)

To a mixture of **34** (660 mg, 1.774 mmol), adenine (480 mg, 3.55 mmol) and PPh_3 (931 mg, 3.55 mmol) in dry dioxane (20 mL) under N_2 at rt was added a solution of DEAD (565 μL, 3.55 mmol) in dry dioxane (10 mL) over a period of 45 min. The reaction mixture was stirred at rt

overnight, concentrated and the residue was chromatographed on silica gel (CH_2Cl_2-MeOH 50:1, then 20:1) to yield crude **35a** (960 mg) as a yellow foam: ^1H NMR ($CDCl_3$) δ -0.12 (s, 3H), -0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.83 (s, 9H), 0.94 (s, 9H), 2.01 - 2.25 (m, 2H), 2.32 (m, 1H), 3.73 (dd, 1H, J = 9.9, 4.8 Hz), 3.82 (dd, 1H, J = 9.9, 4.4 Hz), 3.97 (ddd, 1H, J = 10.2, 7.0, 4.0 Hz), 5.37 (m, 1H), 5.73 (s, 2H), 5.88 (ddd, 1H, J = 9.9, 3.7, 2.5 Hz), 6.06 (ddd, 1H, J = 9.9, 2.2, 1.1 Hz), 7.86 (s, 1H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -5.5 (q), -5.4 (q), -5.0 (q), -4.6 (q), 17.8 (s), 18.3 (s), 25.6 (q), 25.9 (q), 36.5 (t), 47.2 (d), 49.6 (d), 62.9 (t), 64.5 (d), 120.2 (s), 124.4 (d), 134.9 (d), 139.9 (d), 149.8 (s), 153.0 (d), 155.5 (s); LISMS (THGLY/NBA) 490 $(M+H)^+$; HRMS calcd for $C_{24}H_{44}N_5O_2Si_2$ $(M+H)^+$ 490.3034, found 490.3058.

9-[(1*S*,4*R*,5*S*)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine (36)

Crude **35a** was treated with TFA-H_2O (3:1, 40 mL) at rt overnight. The reaction mixture was concentrated and co-evaporated with toluene (2x). The residue was chromatographed on silica gel (CH_2Cl_2-MeOH 20:1, then 5:1) to afford **36** (149 mg, 54% over two steps):

Mp 90 - 92 °C; ^1H NMR (CD_3OD) δ 2.01-2.33 (m, 3H), 3.80 (d, 2H, J = 4.8 Hz), 3.84 (m, 1H), 5.33 (m, 1H), 5.94 (ddd, 1H, J = 9.9, 3.7, 2.6 Hz), 6.13 (ddd, 1H, J = 9.9, 2.5, 1.4 Hz), 8.09 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (CD_3OD) δ 37.3 (t), 47.9 (d), 51.1 (d), 63.1 (t), 64.7 (d), 120.6 (s), 125.3 (d), 136.1 (d), 141.6 (d), 150.4 (s), 153.7 (d), 157.5 (s); UV λ_{max} (MeOH) = 260 nm; LISMS (THGLY/NBA) 262 $(M+H)^+$; HRMS calcd for $C_{12}H_{16}N_5O_2$ $(M+H)^+$ 262.1304, found 262.1359; Anal. Calcd for $C_{12}H_{16}N_5O_2.0.7H_2O$: C 52.62, H 6.04, N 25.57; Found: C 52.62, H5.95, N 25.77.

9-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-hydroxymethyl-cyclohexanyl]adenine (2a)

A mixture of **36** (45 mg, 0.17 mmol) and Pd/C (10%, 40 mg) in MeOH (5 mL) was stirred under H_2 at rt for 24 h. The reaction mixture was cooled to rt and filtered through Celite® and washed with MeOH. The filtrate was concentrated and theireyidue was purified by reversed-phase HPLC (5% CH_3CN in H_2O) to yield **2a** (35 mg, 78%) as a white foam: ^1H NMR (CD_3OD) δ 1.71 (m, 1H), 1.87-2.18 (m, 5H), 2.39 (m, 1H), 3.69 (dd, 1H, J = 14.0, 7.3 Hz), 3.74 (dd, 1H, J = 14.0, 6.9 Hz), 4.12 (m, 1H), 4.87 (m, 1H, overlapped with HOD), 8.18 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (CD_3OD) δ 22.6 (t), 28.7 (t), 36.1 (t), 53.6 (d), 51.9 (d), 63.3 (t), 68.4 (d), 120.4 (s), 141.1 (d), 150.6 (s), 153.5 (d), 157.4 (s); LISMS (THGLY/NBA) 264 $(M+H)^+$; HRMS calcd for $C_{12}H_{18}N_5O_2$ $(M+H)^+$ 264.1460, found 264.1449.

Figure 1. Mechanism of Pd (0) coupling reaction which may yield the desired compound C.

Figure 2. ^1H NMR experiment demonstrates the solvent-dependent conformational equilibrium of compound **34**.

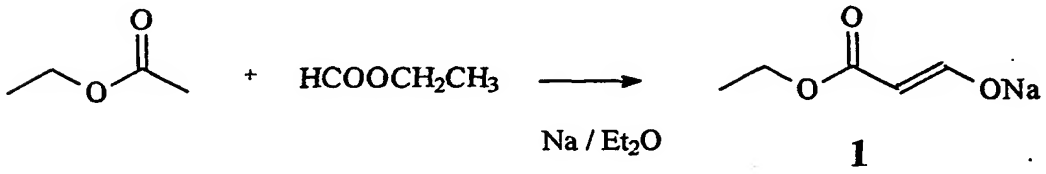
Figure 8 (a) TBDMSCl (1.2 eq), imidazole (2 eq), DMF, r.t., 48% starting from **6a**; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 93 %; (c) DBU, toluene, or KOH, H_2O / THF; (d) DEAD, PPh_3, THF; (e) I_2, PPh_3, imidazole, toluene, reflux, 34%; (f) DBU, toluene, reflux, 68%.

Figure 9 (a) $(CH_3)_2C(OCH_3)_2$, PPTS, acetone/THF (1:2), r.t., 94%; (b) Pd-C (10%), $HCOONH_4$, MeOH, reflux, 100%; (c) PDC, CH_2Cl_2, r.t., 94%; (d) TBAF, THF, r.t.; (e) KF, 18-Crown-6, THF, r.t., 62% **19**; (f) $CeCl_3.7H_2O$, $NaBH_4$, MeOH, 90%; (g) PPh_3, DEAD, AcOH, THF; (h) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 95%; (i) Adenine, NaH, $Pd(PPh_3)_4$, DMF/THF; (j) PPTS, MeOH, r.t., 59%; (k) Bz_2O, DMAP, CH_2Cl_2, 0 °C, 95%.

Figure 10 (a) TBDMSCl (1.2 eq), imidazole (1.5 eq), DMF, r.t., 70%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 100%;

(c) Pd-C(10%), $HCOONH_4$, MeOH, reflux, 76%; (d) MnO_2, CH_2Cl_2, r.t., 48% and 47% recovery of **31**; (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C → r.t., 100%.

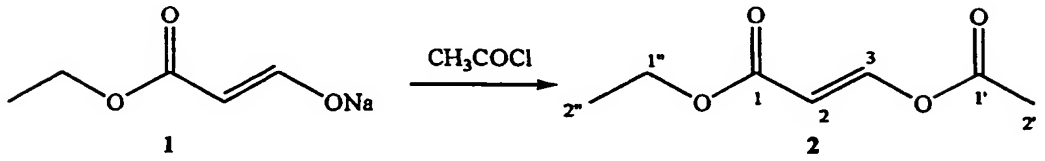
Sodium salt of Ethyl-β-hydroxyacrylate sodium salt (1)



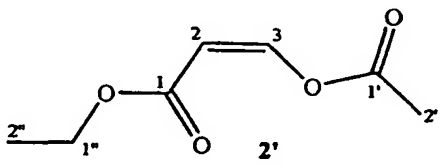
1

In a 1 L three necked flask, under inert atmosphere and equipped with an addition funnel, a well stirred suspension of fresh sodium pieces (23.0 g, 1.0 mol) in dry diethyl ether (400 mL) was prepared. A mixture of ethyl acetate (88.0 g, 1.0 mol) and ethyl formate (74.0 g, 1.0 mol) was added dropwise over a period of 45 minutes. Stirring was continued for an additional 14 hours using an ice bath, avoiding the reaction to become too vigorous. The resulting suspension was kept in the refrigerator for 8 hours, after which it was filtered, washed with dry diethyl ether (100 mL) and dried *in vacuo* to obtain **1** as a pale yellow solid (85.0 g, 61% yield).

Ethyl β-acetoxyacrylate [cis (2′) + trans (2)]



$C_7H_{10}O_4$
Exact Mass: 158.1
Mol.Wt.: 158.2
C, 53.1; H, 6.37; O, 40.47



In a 2 L flask on an ice-bath, under an inert atmosphere, a well stirred suspension of the sodium salt **1** (85.0 g, 616 mmol) was prepared in dry diethyl ether (850 mL), to which acetyl chloride (52.9 mL, 58.2 g, 739 mmol) was added dropwise over 15 minutes. The mixture was stirred for an additional 6 hours, after which it was neutralized with a saturated aqueous solution of $NaHCO_3$ (250 mL). Both phases were separated and the aqueous phase was extracted with diethyl ether (5 x 200 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo* to obtain a residual red oil (59.1 g). Distillation *in vacuo* (70 °C, 1 Torr aprox.) afforded a mixture of **2** and **2′**, as a pure colorless oil (36.5 g, 23 % yield in two steps) with a *cis / trans* proportion of 4:10 (^{1}H-NMR).

analytical data of **2** (*trans* isomer)

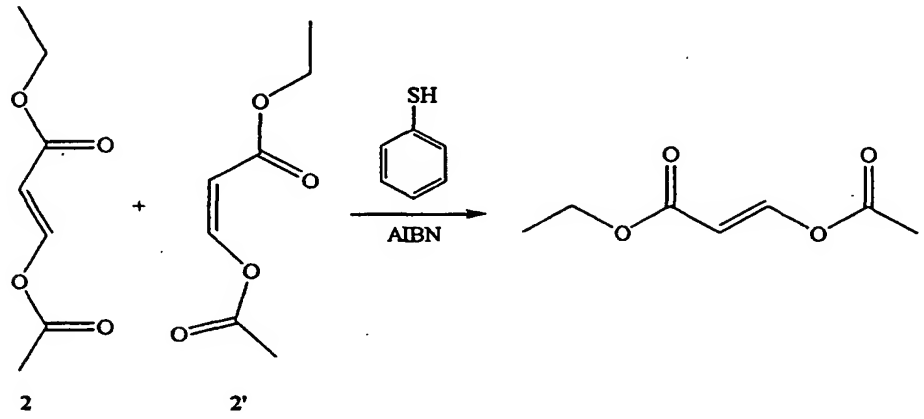
^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.2 Hz, 3H, 2″-H), 2.22 (s, 3H, 2′-H), 4.21 (q, J = 7.2 Hz, 2H, 1″-H), 5.72 (d, J = 12.6 Hz, 1H, 2-H), 8.30 (d, J = 12.6 Hz, 1 H, 3-

H).

analytical data of 2' (*cis* isomer)

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.2 Hz, 3H, 2"-H), 2.28 (s, 3H, 2'-H), 4.20 (q, J = 7.4 Hz, 2H, 1"-H), 5.30 (d, J = 7.3 Hz, 1H, 2-H), 7.54 (d, J = 7.3 Hz, 1H, 3-H).

Isomerization of the *cis/trans* mixture (2/2') to ethyl *trans*-β-acetoxyacrylate (2)

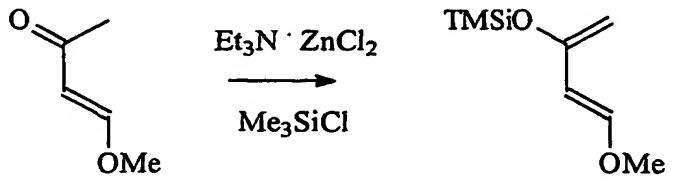


2 2'

In a well-closed flask, under magnetic stirring, the **2/2'** mixture obtained from several operations (52.5 g, 39:100 *cis* / *trans* proportion, 332 mmol) was treated with thiophenol (16.3 ml, 17.5 g, 159 mmol) and 2,2'-azobis(2-methylpropionitrile) (AIBN, 8.31 g, 50.6 mmol) and the mixture was heated to 80 °C for 2.5 hours. The flask was cooled for 2 hours and the crude was diluted with ethyl acetate (400 mL) and washed with an aqueous solution of NaOH 0.01 N (400 mL). The organics were dried over Na_2SO_4, filtered and evaporated *in vacuo* to leave a pale yellow oil. Distillation *in vacuo* (53 °C, 0.5-1.0 Torr) afforded **2** (55.8 g, quantitative yield) with a *cis* / *trans* proportion of 3:97 (^{1}H-NMR), slightly

contaminated with aromatic sulphurated products.

Preparation of (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4)



3 **4**

Under an inert atmosphere anhydrous $ZnCl_2$ (2.52 g, 18.5 mmol) was slowly added under magnetic stirring to triethylamine (distilled over KOH) (145 g, 200 mL, 1.43 mol). The mixture was stirred for 1 hour at room temperature until a fine suspension was obtained. A solution of compound **3** (63.1 g, 630 mmol) in toluene (190 mL) was then added over 5 min, followed by gradual addition of chlorotrimethylsilane (137.0 g, 160 mL, 1.26 mol) over a period of 10 min. An exothermic reaction was noted. After 30 minutes, the temperature was raised to 40 °C and stirring was continued overnight. Following cooling, the reaction mixture was diluted with diethyl ether (1 L), filtered and washed with diethyl ether (4 x 100 mL). The combined filtrate and ether washings were concentrated *in vacuo* to leave a brown oil. Distillation trough a Vigreux column (52 °C, 1.0 Torr) afforded compound **4** in a middle cut, slightly contaminated with compound **3** [80.1 g, 91% purity (^{1}H-NMR), 67% yield of **4**].

NOTE: compound **4** is commercially available (e.g. Aldrich®).

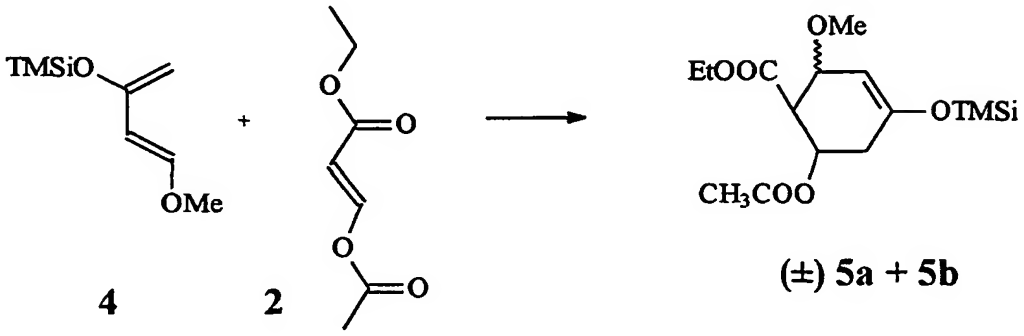
analytical data of **4**.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.23 [s, 9H, $OSi(C\underline{H}_3)_3$], 3.59 (s, 3H, $OC\underline{H}_3$), 4.09 (d, *J* = 8.2 Hz, 2H, 4-H), 5.35 (d, *J* = 512.2 Hz, 1H, 2-H), 6.83 (d, *J* = 12.2 Hz, 1H, 3-H).

Diels-Alder adduct of 2 and 4:

5-*O*-acetyl-4-ethoxycarbonyl-3-*O*-methyl-1-*O*-trimethylsilyl-cyclohexen-1,3,5-triol

[(±) 5a + 5b]



4 **2** **(±) 5a + 5b**

In a 250 mL round bottom flask a small amount of hydroquinone (372 mg) was added under magnetic stirring to a mixture of the Danishefky diene [**4**, 72.9 g, 91% purity (^{1}H-NMR), 385 mmol] and **2** (55.8 g, *cis/trans* 3:97, 353 mmol) and the mixture was heated at 180 °C for 1.5 hours. An additional amount of 372 mg of hydroquinone was added and the reaction mixture was distilled *in vacuo* (94 °C, 3.0 x 10^{-2} mm Hg) to afford a slightly contaminated mixture of **(±) 5a + 5b** (72.0 g, 62% yield), with the substituents at the 4- and 5-position oriented

in *trans*.

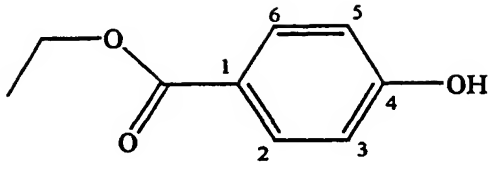
NOTE: Upon increasing the temperature of the distillation bath to 170 °C or higher, different quantities of the phenolic derivative **6** are obtained. The phenol derivative **6** likewise is obtained as the main isolated product when purification on silica gel is undertaken. The addition of fresh hydroquinone right before the distillation seems to avoid the formation of **6**. Compound **6** could not detected by NMR when using this improved procedure.

representative analytical data for the major derivative **(±) 5a** (substituents at 3 and 4 in trans)

^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 1.27 (t, 3H, J = 7.3 Hz), 2.01 (s, 3H), 2.19 (m, 1H), 2.55 (dd, 1H, J = 16.7, 5.5 Hz), 2.77 (dd, 1H, J = 11.4, 8.4 Hz), 3.31 (s, 3H), 4.20 (m, 2H), 4.35 (dm, 1H, J = 8.4 Hz), 4.94 (t, 1H, J = 2.2 Hz), 5.13 (ddd, 1H, J = 11.0, 9.2, 5.9 Hz).

^{13}C NMR ($CDCl_3$) δ 0.06 (q), 14.2(q), 20.8 (q), 35.4 (t), 51.1 (t), 55.4 (q), 60.9 (t), 68.8 (d), 76.5 (d), 103.3 (d), 149.3 (s), 170.0 (s), 172.2 (s).

Ethyl p-hydroxybenzoate (6) : analytical data

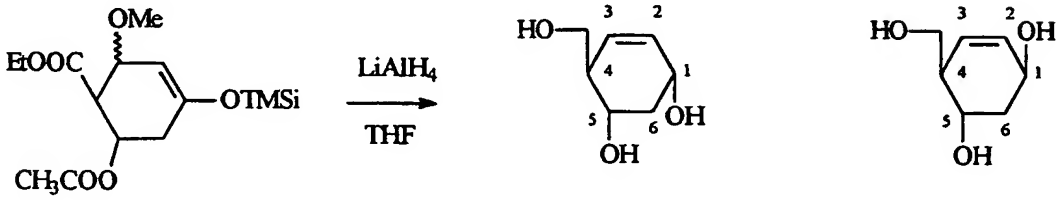


6

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.2 Hz, 3H, -$CH_2\underline{CH_3}$), 4.37 (q, 2H, -$\underline{CH_2}CH_3$), 6.91 [d, J = 8.9 Hz, 2H, 3(5)-H], 7.36 (broad s, 1H, 4-O<u>H</u>), 7.96 [d, J = 8.9 Hz, 2H, 2(6)-H].

^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 14.1 (-$CH_2\underline{C}H_3$), 61.1 (-$\underline{C}H_2CH_3$), 115.3 [C3(5)], 122.2 (C1), 132.0 [C2(6)], 160.7 (C4), 167.6 (C=O).

<u>(±) 4-hydroxymethyl-cyclohex-2-en-1,5-diol (7a)</u>



(±) 5 (±) 7a (±) 7

In a 1L three necked bottom flask on a ice-NaCl bath, a suspension of $LiAlH_4$ (25.0 g, 658 mmol) in dry THF (220 mL) was prepared under magnetic stirring in an inert atmosphere. To this cooled suspension, a solution of the impure mixture of 5a + 5b (27.2 g) in dry THF (85 mL) was added dropwise during 30 minutes. After stirring at 0 °C

for 2 hours, the reaction was continued at room temperature for an additional 19 hours. The mixture became very viscous and was diluted with dry THF (110 mL). After cooling on an ice-NaCl bath, the mixture was treated consecutively and very carefully (equipping the system with a good gas-exit) with water (25 mL), stirring for 15 minutes, with 15% aqueous NaOH (25 ml), stirring for 15 minutes more, and finally with more water (75 ml). A dry granular precipitate was produced, which was easy to filter and wash. The suspension was stirred for 30 minutes and the precipitate was filtered over a layer of Celite®, and washed with water (5 x 100 mL) and ethyl acetate (3 x 100 mL). Both phases were separated and the aqueous phase was washed with ethyl acetate (3 x 100 mL). The aqueous phase was evaporated to dryness to give a brown gummy residue (21.1 g) which was filtered through a silica gel column (210 g) packed with ethyl acetate, eluting with mixtures of EtOAc/MeOH of increasing polarity. The title product **7a** was isolated as a pale yellow oil (3.55g, 24.7 mmol, 30%), preceded by its epimer **7b** (6.44g) as an impure mixture.

analytical data of **7a**

^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 1.48 (td, 1H, J = 11.3, 9.2 Hz), 2.02 - 2.23 (m, 2H), 3.35 (m, 1H), 3.61 (m, 2H), 3.75 (d, 1H, J = 5.8 Hz, OH), 4.01 (t, 1H, J = 4.6 Hz, OH), 4.11 (m, 1H), 4.20 (d, 1H, J = 3.3 Hz, OH), 5.25 (dt, 1H, J = 9.9, 2.0 Hz), 5.58 (dm, 1H, J = 9.9 Hz).

^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 39.7 (t), 45.8 (d), 65.2 (t), 65.9 (d), 69.4 (d), 126.1 (d), 132.4 (d).

LISMS (THGLY/NaOAc) 167 $(M+Na)^+$ ($C_7H_{12}O_3$)

Data of **7b**:

^{1}H NMR (DMSO-d_6) δ 1.37 (td, 1H, J = 11.7, 9.9 Hz), 1.92 - 2.10 (m, 2H), 3.24 - 3.45 (m, 2H), 3.63 (dt, 1H, J =

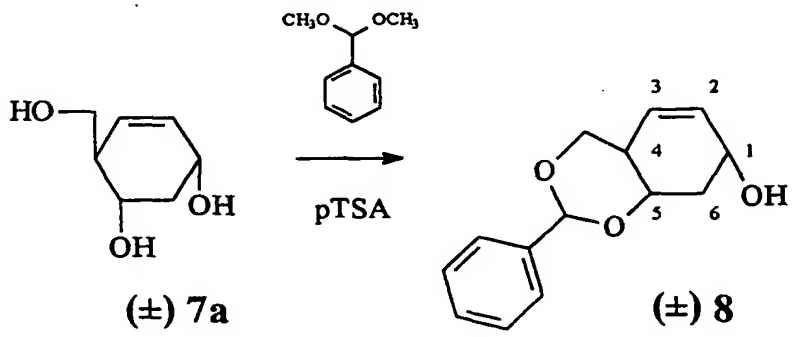
10.2, 4.4 Hz), 4.07 (m, 1H), 4.49 (t, 1H, J = 5.3 Hz, OH), 4.63 (d, 1H, J = 5.1 Hz, OH), 4.70 (d, 1H, J = 5.9 Hz, OH), 5.52 (d, 1H, J = 11.0 Hz), 5.57 (d, 1H, J = 11.0 Hz).

^{13}C NMR (DMSO-d_6) δ 42.0 (t), 47.2 (d), 62.2 (t), 65.9 (d), 66.3 (d), 127.7 (d), 132.8 (d).

LISMS (THGLY/TFA) 145 $(M+H)^+$ ($C_7H_{12}O_3$)

Formation of the ketal of 7a:

(±) 5,7-*O*-benzylidene-4-hydroxymethyl-cyclohex-2-en-1,5-diol (8)



(±) 7a (±) 8

Under an inert atmosphere benzaldehyde dimethyl acetal (6.2 mL, 41.2 mmol) and *p*-toluenesulfonic acid monohydrate (300 mg, 1.58 mmol) were added to a solution of **(±)7a** (4.49 g, 31.1 mmol) in dry dioxane (140 mL). The mixture was stirred at room temperature for 24 hours and subsequently poured into ethyl acetate (100 mL), washed with water (250 mL), dried over Na_2SO_4 and concentrated to give a white residue (8.91 g). Chromatographic purification on silica gel (270 g) eluting with mixtures of hexane/EtOAc of increasing polarity afforded the desired product **8** as a white crystalline solid (5.06 g,

70% yield, 80% yield based on recovered **7a**).

The aqueous phase was evaporated to dryness, to recover the starting material **7a** (600 mg, 13 % recovery).

analytical data of **8a**

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.60 (d, J = 7.3 Hz, 1H, OH), 1.80 (ddd, 1H, 6-H_a), 2.53 (ddd, 1H, 6-H_e), 2.60 (m, 1H, 4-H), 3.61 (t, J = 11.2 Hz, 1H, 7-H_a), 3.68 (ddd, 1H, 5-H), 4.26 (dd, J = 10.7 and 4.4 Hz, 1H, 7-H_e), 4.53 (m, 1H, H-1), 5.42 (ddd, J = 9.7 Hz, 1H, 2-H), 5.59 (s, 1H, PhC<u>H</u>), 5.74 (ddd, J = 9.8 Hz, 1H, 3-H), 7.31-7.40 and 7.48-7.53 (m, 5H, arom-H).

^{13}C-NMR (500 MHz, $CDCl_3$) δ: 38.6 (C-6), 40.1 (C-4), 68.0 (C-1), 70.7 (C-7), 77.7 (C-5), 102.2 (PhCH), 125.0 (C-2), 126.2 (ar-C_o), 128.3 (ar-C_m), 129.0 (ar-C_i), 132.7 (C-3), 138.1 (ar-C_p).

LISMS (GLY/TFA) 233 $(M+H)^+$ ($C_{14}H_{16}O_3$)

Additional amounts of the desired **8a** can be obtained using the other epimer **7b**, using an oxidation - reduction cycle as outlined below.

Therefore, the crude **7b** (2.3 g, 14.58 mmol) was treated with benzaldehyde dimethyl acetal (3.28 mL, 21.87 mmol) in the presence of p-toluenesulfonic acid monohydrate (PTSA, 138 mg, 0.73 mmol) in 1,4-dioxane (30 mL) at r.t. for two days. Ice was added and the mixture was stirred at r.t. for 0.5 hr and extracted with EtOAc (3x). The combined organic solvents were washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified on silica gel (hexane /EtOAc 1:1) to afford a mixture of **8b** and **8a** (3:1, 1.2 g) as a light yellow solid.

The mixture of **8a/8b** (3:1, 415 mg, 1.79 mmol) and MnO_2 (1.56 g, 17.9 mmol, 10 eq) in dry CH_2Cl_2 (15 mL)

was stirred at rt for 21 hrs. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated and the residue was chromatographed on silica gel (hexane - EtOAc 2:1) to afford **9** (340 mg, 83%) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ 2.65 (dd, 1H, *J* = 16.4, 13.1 Hz), 2.83 (m, 1H), 2.95 (dd, 1H, *J* = 16.4, 4.8 Hz), 3.79 (t, 1H, *J* = 11.1 Hz), 4.04 (ddd, 1H, *J* = 13.1, 9.2, 4.8 Hz), 4.45 (dd, 1H, J = 11.1, 4.8 Hz), 5.63 (s, 1H), 6.13 (dd, 1H, *J* = 9.9, 2.9 Hz), 6.58 (dd, 1H, *J* = 9.9, 1.8 Hz), 7.39 (m, 3H), 7.51 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 39.9 (d), 44.3 (t), 69.2 (t), 77.4 (d), 101.7 (d), 126.1 (d), 128.4 (d), 129.2 (d), 132.1 (d), 137.5 (s), 144.9 (d), 196.8 (s).

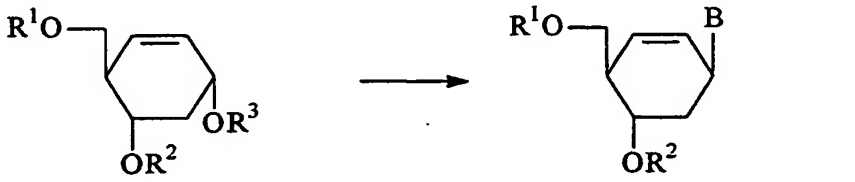
LISMS (NBA) 231 $(M+H)^+$. ($C_{14}H_{14}O_3$)

Conversion of **9** to **8a**:

To a solution of **9** (340 mg, 1.5 mmol) in MeOH (15 mL) at rt was addded $CeCl_3.7H_2O$ (838 mg, 2.25 mmol, 1.5 eq). After stirring at rt for 1 hr, $NaBH_4$ (68 mg, 1.8 mmol, 1.2 eq) was added in portions. The reaction was stirred at rt for 2 hrs and quenched with crushed ice. The resulting mixture was stirred at rt for 0.5 hr and concentrated. The residue was taken into ethyl acetate and washed with water and brine, dried over sodium phosphate and concentrated. The residue was chromatographed on silica gel (hexane - EtOAc 5:1 and 1:1) to give **8a** as a white solid which proved identical to the previous material.

The product **8a**, or its analogues, either under their racemic form, or under the form of their separated isomers, as represented by the general structure **III**, can be used for synthesis of cyclohexenyl nucleoside

analogues of general structure **IV**, according to standard procedures for alkylation of heterocyclic bases. Hereto, in the general structure **III**, R^1 and R^2 are representing protecting groups (e.g. R_1, R_2 = C_6H_5-CH=), and R^3 represents a leaving functionality (e.g. R^3 = SO_2CH_3, SO_2CF_3, $SO_2C_6H_4CH_3$, $SO_2C_6H_4CH_3$, $SO_2C_6H_4Br$) enabling nucleophilic substitution reactions, or R^3 represents hydrogen, to be used in Mitsunobu reactions.



(III) **(IV)**

example:

N^2-Benzoyl-9-(5-hydroxy-4-hydroxymethyl-2-cyclohexenyl)guanine ((±) 11)

To a mixture of **(±) 8a** (696 mg, 3 mmol), 2-amino-6-chloropurine (1.02 g, 6 mmol) and triphenyl phosphine (PPh_3, 1.57 g, 6 mmol) in dry 1,4-dioxane (30 mL) was added slowly a solution of DEAD (945 mL, 6 mmol) in dry 1,4-dioxane (10 mL). The reaction was stirred at r.t. overnight and concentrated. The residue was taken on silica gel and chromatographed on silica gel (CH_2Cl_2 / MeOH 100:1 and 50:1) to afford the crude **10** (2 g) and the N_7-epimer (140 mg) as a white solid.

The crude **10** (2 g) was treated with TFA/H_2O (3:1, 20 mL) at r.t. for 2 days. The reaction mixture was

concentrated and coevaporated with toluene. The residue was chromatographed on silica gel (CH_2Cl_2 / MeOH 50:1 and 10:1) to produce **(±) 11** (220 mg, 27 % overall yield starting from **8a**).

The spectrum of **11** is identical to that previously reported.

Table I

Antiviral activity of D-cyclohexenyl G and L-cyclohexenyl G in comparison with approved antiviral drugs: 50% inhibitory concentration (IC_{50}) values are given in µg/ml.

Virus	D-cyclohexenyl G		L-cyclohexenyl G		Brivudin	Acyclovir	Ganciclovir	Cidolovir
	Activity	Selectivity index	Activity	Selectivity index				
HSV-1 (KOS) [a]	0.002 [b]	> 2.10^5	0.003 [b]	> 5.10^3	0.001 [b]	0.01 [b]	0.001 [b]	ND
HSV-1 (F) [a]	0.002 [b]	> 2.10^5	0.003 [b]	> 5.10^3	0.001 [b]	0.003 [b]	0.001 [b]	ND
HSV-1 (McIntyre) [a]	0.004 [b]	> 1.10^5	0.004 [b]	> 4.10^3	0.001 [b]	0.005 [b]	0.001 [b]	ND
HSV-2 (G) [a]	0.05 [b]	> 8.10^3	0.07 [b]	> $2.2\ 10^2$	> 80 [b]	0.02 [b]	0.002 [b]	ND
HSV-2 (196) [a]	0.07 [b]	> 5.10^3	0.1 [b]	> $1.6\ 10^2$	> 80 [b]	0.02 [b]	0.001 [b]	ND
HSV-2 (Lyons) [a]	0.07 [b]	> 5.10^3	0.07 [b]	> $2.2\ 10^2$	> 80 [b]	0.02 [b]	0.001 [b]	ND
HSV-1 (TK⁻ KOS ACV^r) [a]	0.38 [b]	> 1.10^3	1.28 [b]	> 12	> 80 [b]	9.6 [b]	0.48 [b]	ND
HSV-1 (TK⁻/TK⁺ VMW1837) [a]	0.01 [b]	>4.10^4	0.01 [b]	> $1.6\ 10^3$	> 80 [b]	0.07 [b]	0.01 [b]	ND
VZV (YS) [c]	0.49 [d]	> 40	1.2 [d]	> 16	0.03 [d]	1.1 [d]	ND	ND
VZV (OKA) [c]	0.64 [d]	> 30	1.9 [d]	> 10	0.003 [d]	0.8 [d]	ND	ND
VZV (TK⁻ 07/1) [c]	2.1 [d]	> 10	5.8 [d]	> 3	> 20 [d]	13 [d]	ND	ND
VZV (TK⁻ YS/R) [c]	2.8 [d]	> 7	6.8 [d]	> 3	> 50 [d]	28 [d]	ND	ND
CMV (AD 169) [c]	0.6 [d]	> 30	1.5 [d]	> 13	ND	ND	0.6 [d]	0.08 [d]
CMV (Davis) [c]	0.8 [d]	> 25	1.7 [d]	> 12	ND	ND	0.8 [d]	0.2 [d]

(a) Activity determined in E_6SM cell cultures
(b) Minimum inhibitory concentration (µg/ml) required to reduce virus-induced cytopathogenicity by 50%
(c) Activity determined in HEL cells
(d) Inhibitory concentration (µg/ml) required to reduce virus plaque formation by 50%. Virus input was 20 plague forming units (PFU)
ND : not determined

Table II

Cytotoxicity of D-cyclohexenyl G and L-cyclohexenyl G in four different cell lines (concentrations in µg/ml)

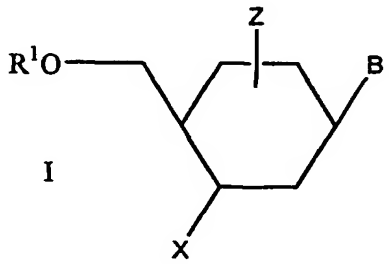
Cell line	D-cyclohexenyl G	L-cyclohexenyl G	Brivudin	Acyclovir	Ganciclovir	Cidofovir
HeLa[a]	400	400	≥ 400	ND	ND	ND
Vero[a]	400	400	≥ 400	ND	ND	ND
E_6SM[a]	> 400	> 16	≥ 400	≥ 400	> 100	ND
HEL[b]	> 20	> 20	> 50	> 50	> 50	> 50
HEL[c]	11	> 20	> 200	> 200	> 50	> 50

(a) Minimum cytotoxic concentration causing a microscopically detectable alteration of cell morphology

(b) Cytotoxic concentration required to reduce cell growth by 50%

CLAIMS

1. A six membered, at least partially unsaturated, carbocyclic nucleoside compound, including the (-) enantiomer, the (+) enantiomer, and pharmaceutically acceptable salts and esters thereof, the compounds represented by the general formula I:



I

wherein:

- Z represents the presence of 1 or more double bonds in the six membered carbocyclic ring,

- B is a heterocyclic ring selected from the group consisting of pyrimidine and purine bases,

- X is a hydrogen, azido, F, or OR^2,

- R^1 and R^2 are the same or different and represent the same or different protecting groups,

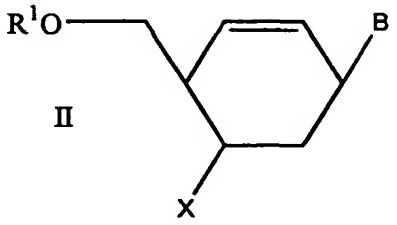
hydrogen, alkyl, alkenyl, acyl or phosphate moieties wherein;

- the alkyl moiety is a saturated, substituted or unsubstituted straight or branched chains hydrocarbon radical having from 1 to 20, for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms,

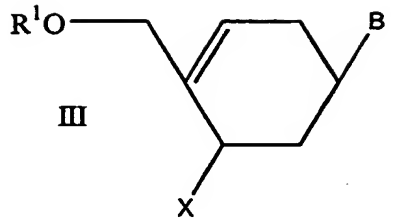
- the alkenyl moiety is an unsaturated congener of the alkyl group and,

- the acyl moiety is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl substituted benzoyl or naphtoyl.

2. A six membered, at least partially unsaturated, carbocyclic nucleoside compound, according to claim 1, being a cyclhexenyl nucleoside compound having the general formula II or III, preferably II:

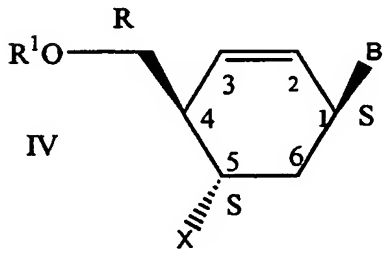


II

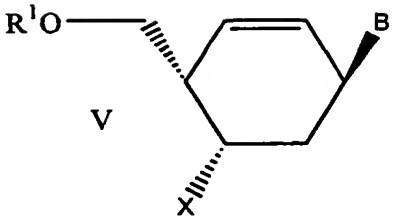


III

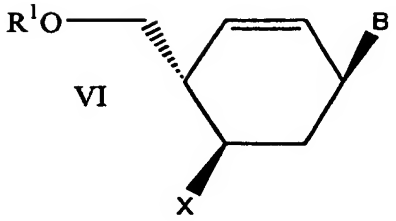
3. Compound according to claims 1 or 2, selected from the following group of compounds represented by the formulas IV-X':



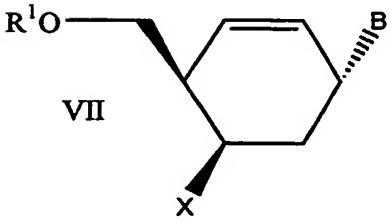
IV



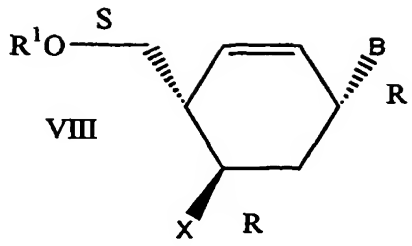
V



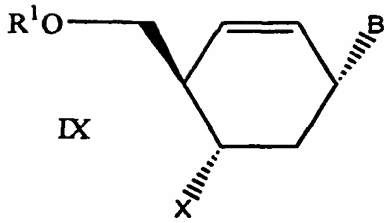
VI



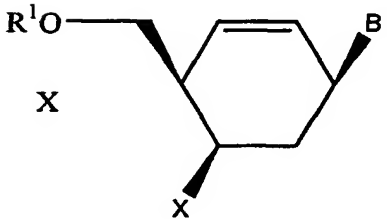
VII



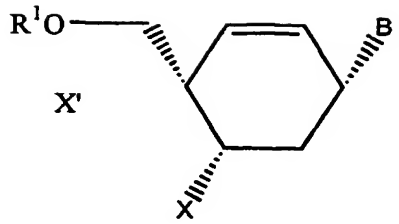
VIII



IX



X



4. Compound according to any of the preceding claims, wherein the C_1 bearing B substituent and the C_5 bearing X substituent both have the (S)-configuration, and the C_4 bearing $-OR^1$ substituent has the (R)-configuration, as depicted by formula IV in claim 3.

5. Compound according to claims 1,2 or 3, wherein the C_1 bearing B substituent and the C_5 bearing X substituent both have the (R)-configuration, and the C_4 bearing $-OR^1$ substituent has the (S)-configuration, as depicted by formula VIII in claim 3.

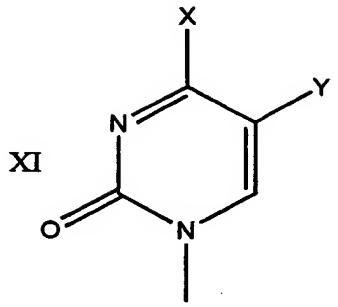
6. Compound according to any of the claims 1-4, wherein X is represented by a hydroxyl group in the (S)-configuration.

7. Compound according to any of the claims 1, 2,3 and 5, wherein X is hydroxyl in the (R)-configuration.

8. Compound according to any of the preceding claims wherein B is derived from the group consisting of pyrimidine bases.

9. Compound according to claim 7 wherein the

pyrimidine base has the general formula XI:



wherein X is chosen from the following;

- OH, NH_2, NHQ,

wherein;

- Q is selected from the following;

OH or C_{1-5} alkyl,

-Y is selected from the following;

H, F, Cl, Br, I, C_{1-5} alkyl, haloethyl or CH=CH-R, wherein R represents hydrogen, halogen or C_{1-5} alkyl, and wherein haloethyl contains from 1 to 4 F, CI or Br atoms.

10. Compound according to any of the preceding claims wherein B is selected form the group consisting of substituted and unsubstituted adenine, guanine, 2,6-diaminopurine, hypoxanthine and xanthine.

11. Compound according to any of the preceding claims wherein the B is selected from the group of aza, deaza deoxy or deamino analogues of the heterocyclic

rings, as defined in any of the claims 8-10.

12. Compound according to any of the preceding claims wherein the protecting group comprises a silyl protecting group, preferably TBDMS, and/or a benzoyl protecting group and or a C6H5-CH= group.

13. Compound according to any of the preceding claims 1-11 selected from:

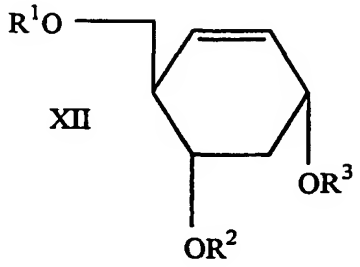
- 9-[1S,4R,5S)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl] guanine
- 9-[1R,4S,5R)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl].

14. Compound according to any of the claims 1-11 selected from the following group:

- 9-[(1S,4R,5S)-5-(tert-Butyldimethylsilyloxy)-4-(tert-butyldimethylsilyloxymethyl)-2-cyclohexenyl]adenine
- 9-[(1S,4R,5S)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine
- 9-[(1S,4R,5S)-5-(tert-butyldimethylsilyloxy)-4-(tert-butyldimethylsilyloxymethyl)-2-cyclohexenyl]-2-amino-6-chloropurine
- 9-[(1S,4R,5S)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine
- 9-[(1R,4S,5R)-5-Benzoyloxy-4-benzoyloxymethyl-2-cyclohexenyl]adenine
- 9-[(1R,4S,5R)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine
- 9-[(1R,4S,5R)-5-Benzoyloxy-4-benzoyloxymethyl-2-cyclohexenyl]guanine
- 9-[(1R,4S,5R)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine

15. Process for providing a compound, the (-) enantiomer, the (+) enantiomer, and pharmaceutically acceptable salts and esters thereof according to any of the preceding claims, said process comprising the steps of:

- providing cyclohexenyl compound of the general formula XII;



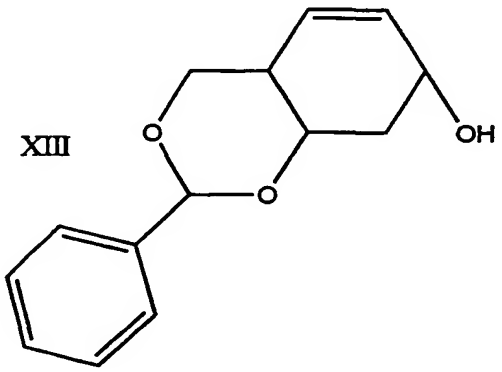
- wherein R^1 and R^2 are protecting groups and R^3 is a leaving group or an Hydrogen atom, followed by the step of substituting the OR^{-3} group by a pyrimidine or purine base.

16. Process according to claim 15 wherein R^3 is hydrogen and wherein a Mitsunobo type reaction is utilised.

17. Process according to claim 15 wherein R^3

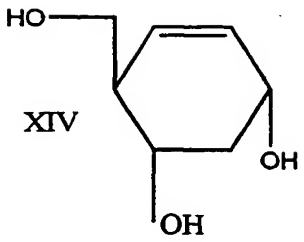
is a leaving group enabling nucleophilic substitution.

18. Process according to any of the preceding claims 15-17 wherein the compound of general formula XII has the chemical formula XIII;



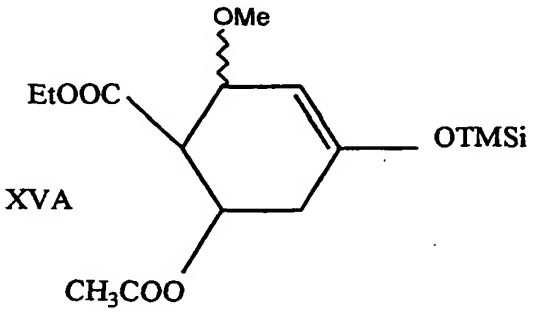
or analogues thereof either in a racemate form or separated isomers thereof.

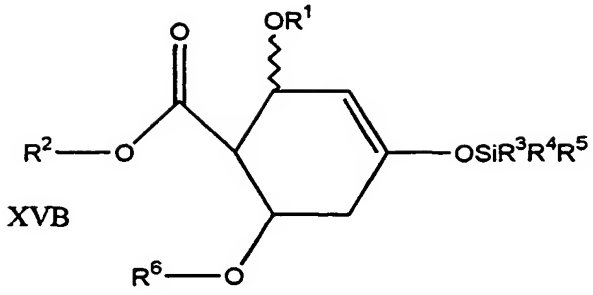
19. Process according to any of the preceding claims 15-18 wherein compound XIII is provided by reacting (±) 4-hydroxymethyl- cyclohex-2-en-1,5 Diol of formula XIV;



with a benzaldehyde analogue and a lewis acid, preferably being benzaldehyde dialkyl acetal, most preferably dimethyl acetal, and p-toluenesulfonic acid.

20. Process according to any of the preceding claims 15-19 wherein compound XIV is provided by the reduction of compound XVA or XVB, preferably utilising lithium aluminium hydride or an equivalent thereof as reducing agent;





XVB

wherein for XVB:

R^1 and R^2 are alkyl or alkenyl moieties,

wherein:

- R^1 and R^2 are the same or different, and

- alkyl is a saturated, substituted or unsubstituted hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms and being straight or branched chain, and

- alkenyl is the unsaturated congener of the alkyl group, and

R^3, R^4 and R^5 are alkyl, alkenyl or aryl moieties, wherein:

- R^3, R^4 and R^5 are the same or different, and

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms and

- alkenyl is the unsaturated congener of the alkyl group, and

- aryl represents phenyl or substituted phenyl, and

R^6 is a alkyl, alkenyl or acyl moiety, wherein:

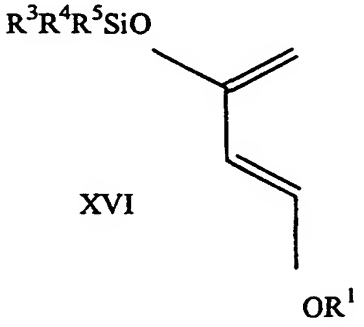
- alkyl is a saturated, substituted or unsubstituted hydrocarbon straight or branched chain radical having from having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms,

- alkenyl is the unsaturated congener of the alkyl group, and

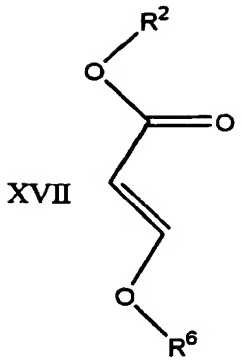
- acyl is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl, substituted benzoyl or naphtoyl.

21. Process according to claim 20 wherein compound XVA or XVB is provided by a diels-alder reaction, by the cyclo addition of a suitable diene and dienophile wherein preferably the diene and dienophile are heated together in the presence of hydroquinone.

22. Process according to claim 21 wherein the diene has the following chemical structure XVI, and the dienophile has the following chemical structure XVII, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claim 20;

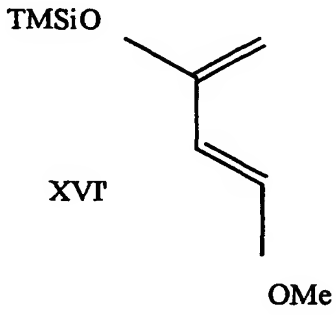


XVI

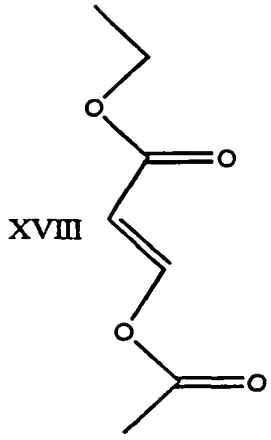


XVII

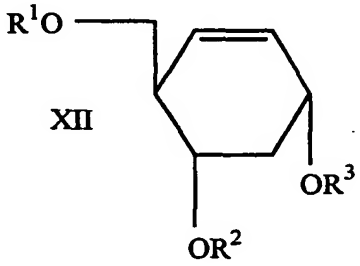
23. Process according to claim 22 wherein the diene has the chemical structure XVI' and the dienophile has the chemical structure XVIII;

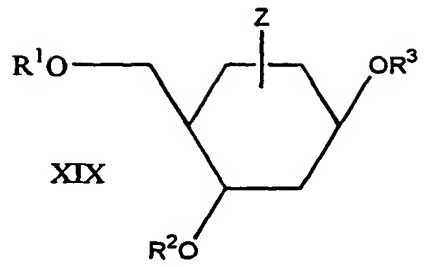


XVI'



24. A six membered, at least partially unsaturated, carbocyclic nucleoside compound, including the (-) enantiomer, the (+) enantiomer, and pharmaceutically acceptable salts and esters thereof, the compounds represented by the general formula XII or XIX;





XIX

wherein:

- Z represents the presence of 1 or more double bonds in the carbocyclic ring,

- R^1 and R^2 are protecting groups and R^3 is a leaving group or an Hydrogen atom.

25. Compound according to claim 24 wherein;

R^1 and R^2 are the same or different and hydrogen, alkyl, alkenyl, acyl or phosphate moieties are represented, or R^1 and R^2 represent a cyclic protecting group; wherein:

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms, and

- alkenyl is the unsaturated congener of the alkyl group, and

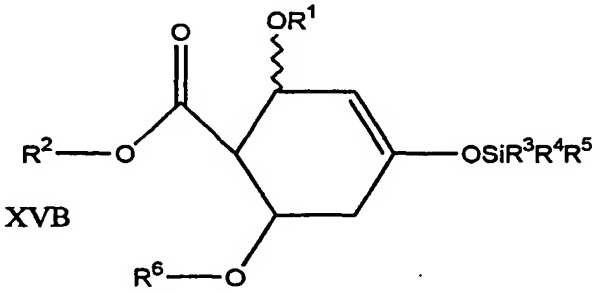
- acyl is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl, substituted benzoyl or naphtoyl; and

R^3 represents a hydrogen, an alkylsulfonyl or an arylsulfonyl moiety, wherein:

- alkyl is a saturated, substituted or unsubstituted hydrocarbon radical having from 1 to 6 carbon atoms and straight or branched chain, and

- aryl represents phenyl or substituted phenyl, and

26. A cyclohexenyl compound, including the (-) enantiomer, the (+) enantiomer, and pharmaceutically acceptable salts and esters thereof, the compound represented by the general formula XVB;



XVB

wherein R^1 and R^2 are alkyl or alkenyl moieties, wherein:

- R^1 and R^2 are the same or different, and

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4 carbon atoms,

- alkenyl is the unsaturated congener of the alkyl group, and

R^3, R^4 and R^5 are alkyl, alkenyl or aryl

moieties, wherein:

- R^3, R^4 and R^5 are the same or different, and

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4 carbon atoms and,

- alkenyl is the unsaturated congener of the alkyl group, and

- aryl represents phenyl or substituted phenyl, and

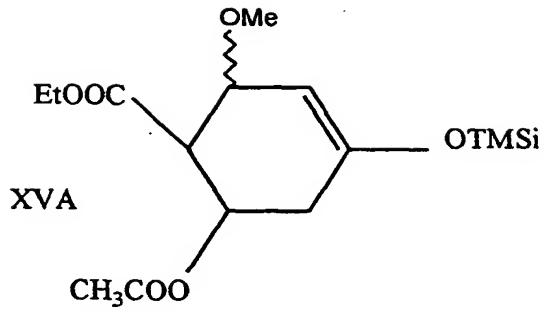
R^6 is a alkyl, alkenyl or acyl moiety, wherein:

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4 carbon atoms, and

- alkenyl is the unsaturated congener of the alkyl group, and

- acyl is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl, substituted benzoyl or naphtoyl.

27. Compound according to claim 26 having the formula XVA being; 5-O-acetyl-4-ethoxycarbonyl-3-O-methyl-1-O-trimethylsilyl-cyclohexen-1,3,5-triol and its isomers;



XVA

28. (±) 4-hydroxymethyl-cyclohex-2-en-1,5-diol.

29. (1*R*, 4*R*, 5*S*)-4-hydroxymethyl-cyclohex-2-en-1,5-diol.

30. (1*S*, 4*S*, 5*R*)-4-hydroxymethyl-cyclohex-2-en-1,5-diol.

31. (±) 5,7-*O*-benzylidene-4-hydroxymethyl-cyclohex-2-en-1,5-diol.

32. (1*R*, 4*R*, 5*S*)-5,7-*O*-benzylidene-4-hydroxymethyl-cyclohex-2-en-1,5-diol.

33. (1*S*, 4*S*, 5*R*)-5,7-*O*-benzylidene-4-hydroxymethyl-cyclohex-2-en-1,5-diol.

34. Compound according to any of the preceding claims 24-26 selected from the following group:

- (4*S*,5*R*)-5-Benzoyloxy-4-benzoyloxymethyl-cyclohex-2-en-1-one,
- (1S,4*S*,5*R*)-5-Benzoyloxy-4-benzoyloxymethyl-cyclohex-2-en-1-ol,
- (4*R*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-tert-butyldimethylsilyloxy-cyclohex-2-en-1-one,

- (1R,4*R*,5*S*)-5-(tert-Butyldimethylsilyloxy)-4-(tert-butyldimethylsilyloxymethyl)-cyclohex-2-en-1-ol.

35. Compound according to any of the claims 1-14, 24-34 obtainable according to the process according to any of the claims 15-23.

36. Pharmaceutical composition comprising a compound according to any of the claims 1-14, 24-34.

37. A pharmaceutical composition as claimed in any of the claims 1-14, 24-34, having antiviral activity towards herpetic viruses selected but not limited from the group consisting of herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), Varicella zoster virus (VZV), and cytomegalovirus (CMV), as well as towards pox viruses, e.g. vaccinia virus (VV).

38. A pharmaceutical composition as claimed in claim 37 comprising said active ingredient in a concentration ranging from about 0.1-100 % by weight.

39. A pharmaceutical composition as claimed in claim 38, having the form which is selected from the group consisting of powders, suspensions, solutions, sprays, emulsions, unguents and creams.

40. The use of a compound according to any of the claims 1-14, 24-34 as a pharmaceutical preferably anti-viral agent.

41. The use of a compound according to any of the claims 1-14, 24-34 as an agent having biological activity.

42. The use of a compound according to any of the claims 1-14, 24-34 as an agent having antiviral activity towards herpes viruses, pox viruses and related viruses.

43. The use of a compound according to any of the claims 1-14, 24-34 for the preparation of a pharmaceutical composition having antiviral activity towards herpes viruses, pox viruses and related viruses.

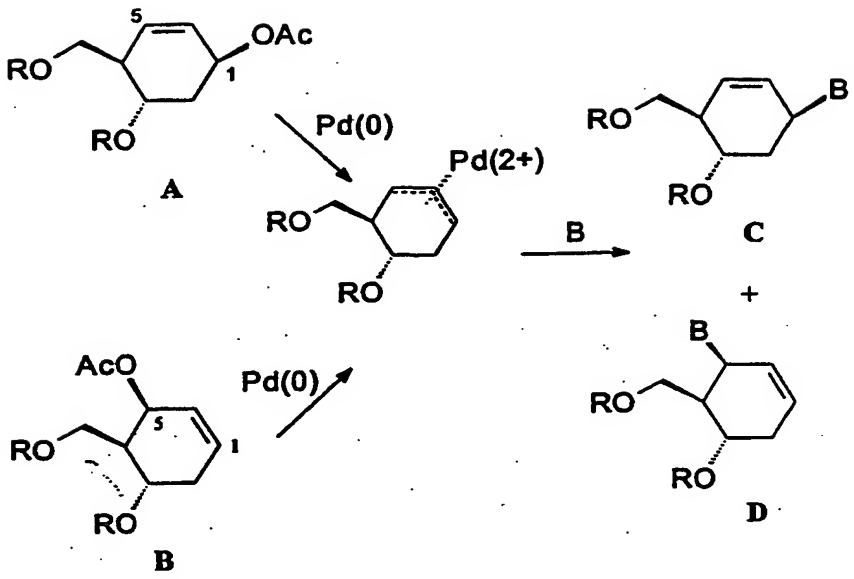
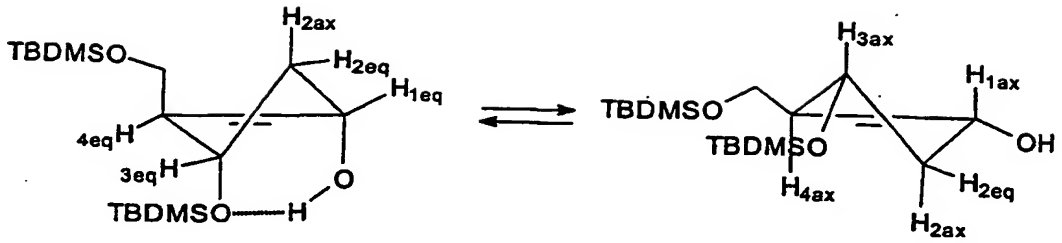


FIG. 1



A 34 B

in $CDCl_3$

$J_{1eq, 2eq}$ = 4.5 Hz
$J_{1eq, 2ax}$ = 3.9 Hz
$J_{3eq, 2eq}$ = 2.6 Hz
$J_{3eq, 2ax}$ = 5.3 Hz
$J_{3eq, 4eq}$ = 3.4 Hz
$J_{1eq, OH}$ = 9.8 Hz

in DMSO-d_6

$J_{1ax, 2ax}$ = 11.7 Hz
$J_{3ax, 2ax}$ = 11.7 Hz
$J_{3ax, 2eq}$ = 3.2 Hz
$J_{3ax, 4ax}$ = 8.5 Hz
$J_{1ax, OH}$ = 5.9 Hz

FIG. 2

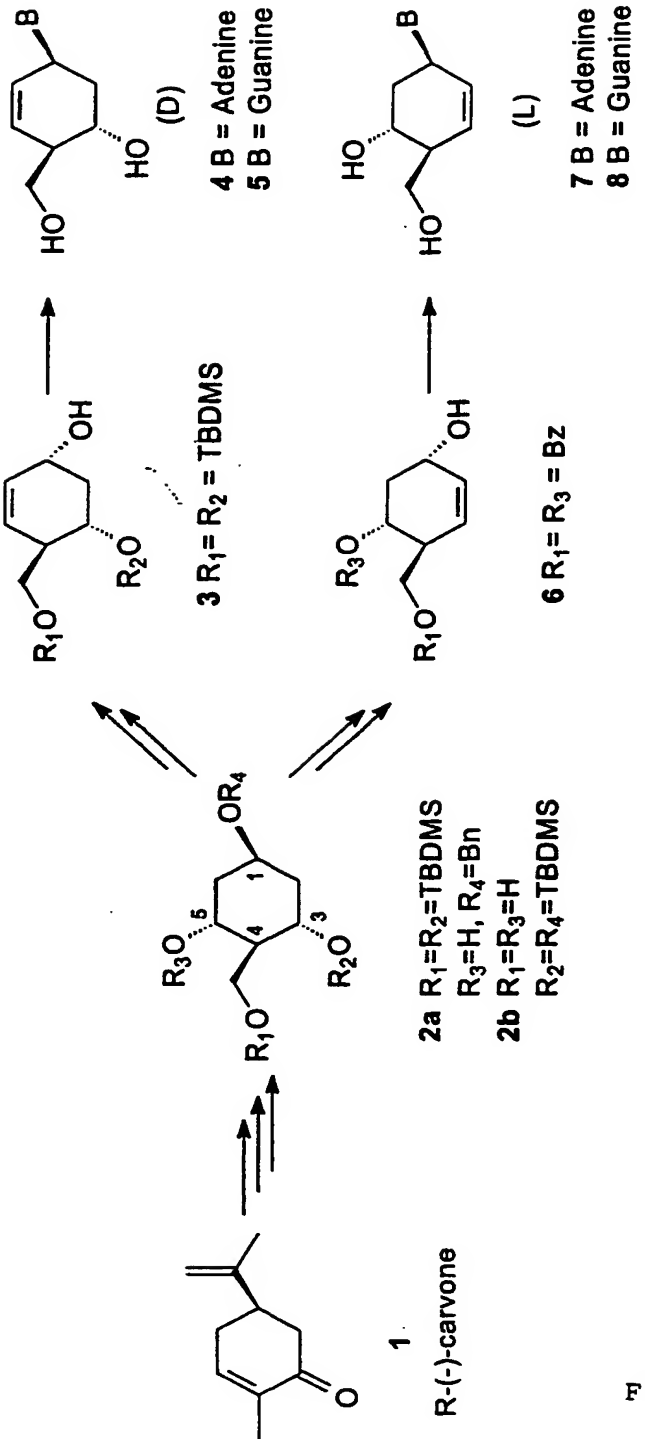

B
HO
HO
(D)
4 B = Adenine
5 B = Guanine
OH
R2O
R1O
3 R1= R2 = TBDMS
B
HO
HO
(L)
7 B = Adenine
8 B = Guanine
OH
R3O
R1O
6 R1= R3 = Bz
OR4
R3O
R2O
R1O
2a R1=R2=TBDMS
R3=H, R4=Bn
2b R1=R3=H
R2=R4=TBDMS
O
1
R-(-)-carvone

FIG. 3

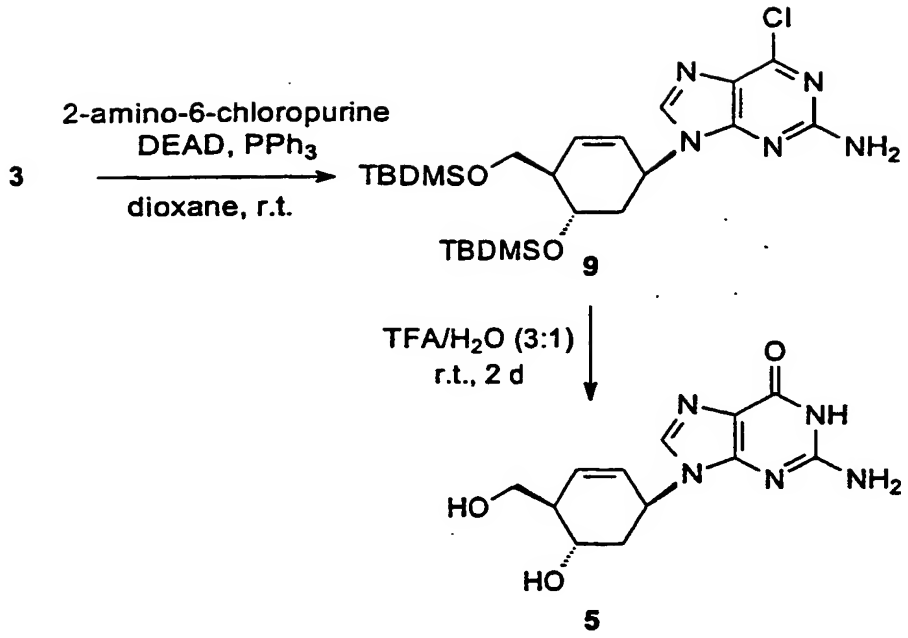
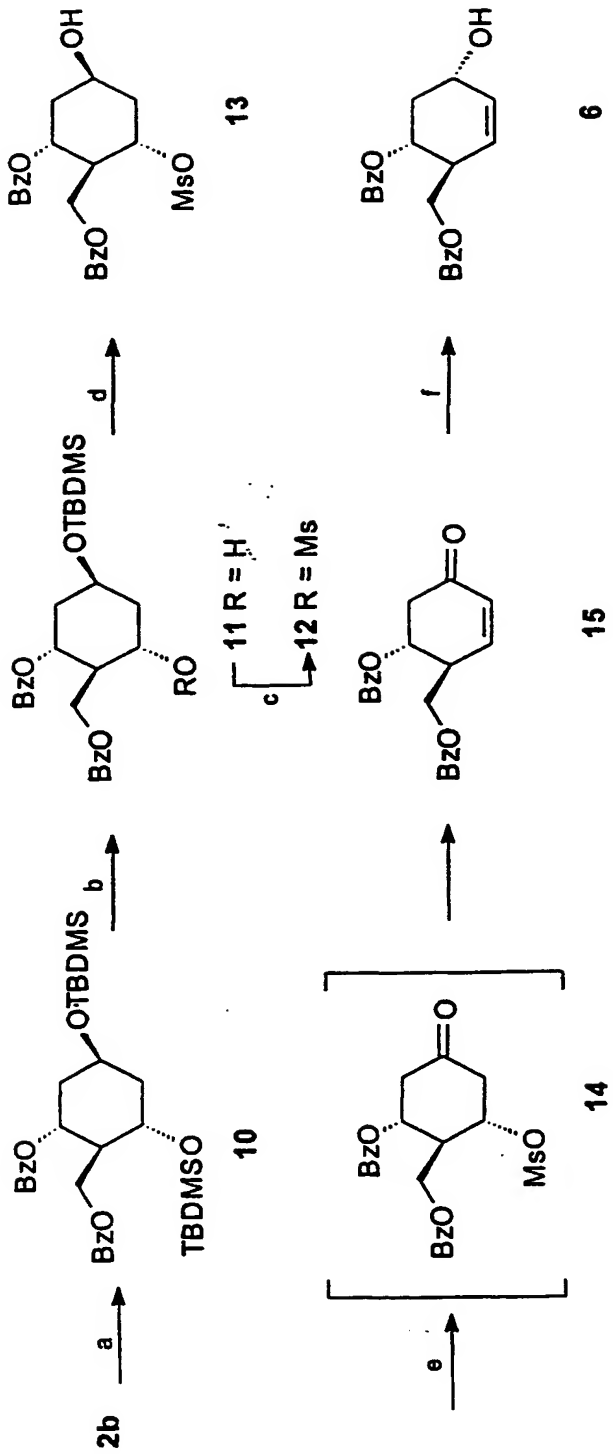

3
2-amino-6-chloropurine
DEAD, PPh3
dioxane, r.t.
TBDMSO
TBDMSO
9
TFA/H2O (3:1)
r.t., 2 d
HO
HO
5
46% overall yield starting from 3

FIG. 4



a. Bz_2O, DMAP, CH_2Cl_2, 0 °C, 98%; b. TBAF (1eq), THF, r.t., 74%; c. MsCl, Et_3N, CH_2Cl_2, 0°C, 98%; d. TBAF, THF, r.t., 86%; e. PDC, CH_2Cl_2, r.t., 68%; f. $NaBH_4$, $CeCl_3.7H_2O$, MeOH, r.t., 75%.

FIG. 5

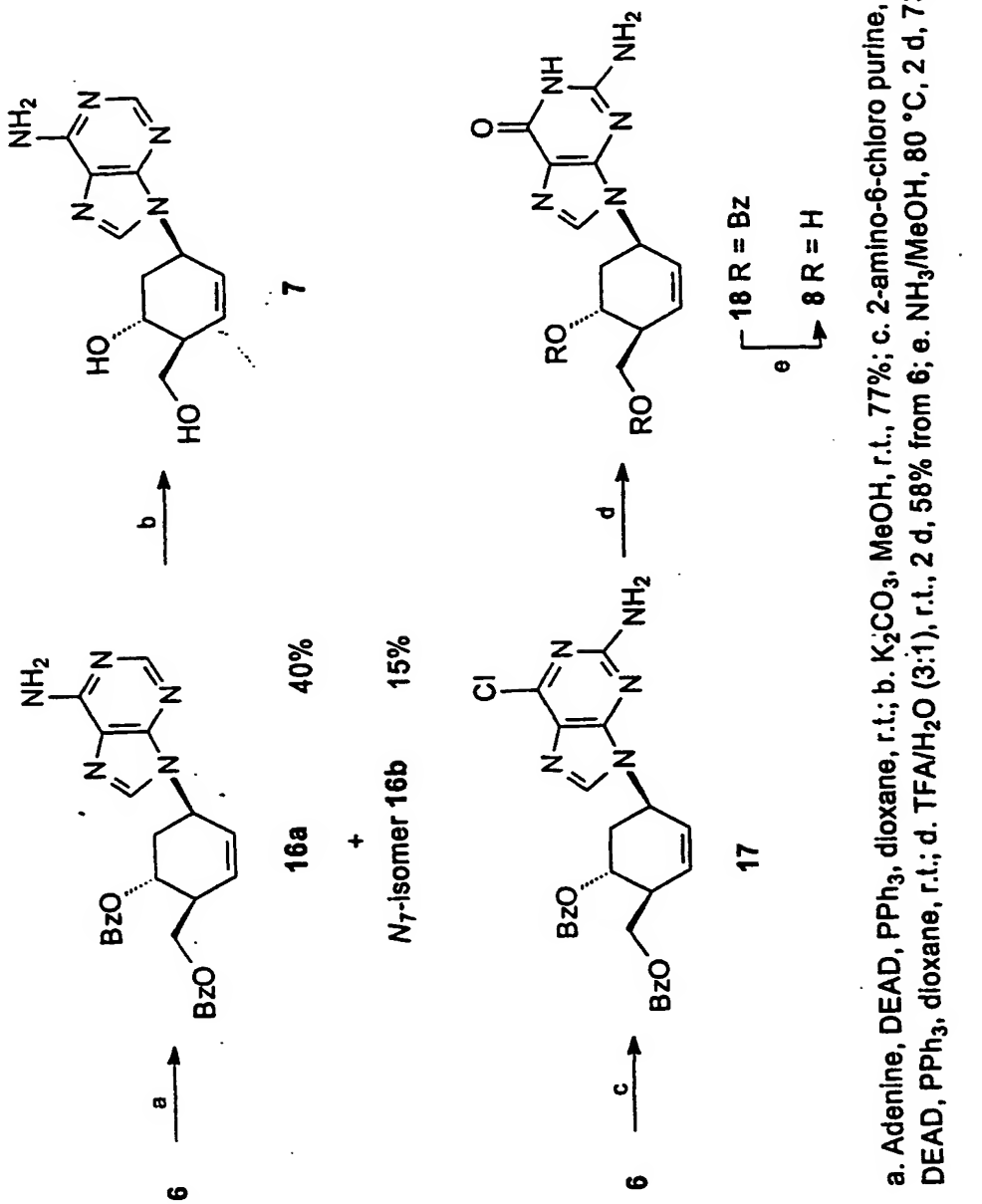

6
a
16a 40%
+
N7-isomer 16b 15%
7
b
6
c
17
d
18 R = Bz
e
8 R = H
a. Adenine, DEAD, PPh3, dioxane, r.t.; b. K2CO3, MeOH, r.t., 77%; c. 2-amino-6-chloro purine, DEAD, PPh3, dioxane, r.t.; d. TFA/H2O (3:1), r.t., 2 d, 58% from 6; e. NH3/MeOH, 80 °C, 2 d, 73%.

FIG. 6

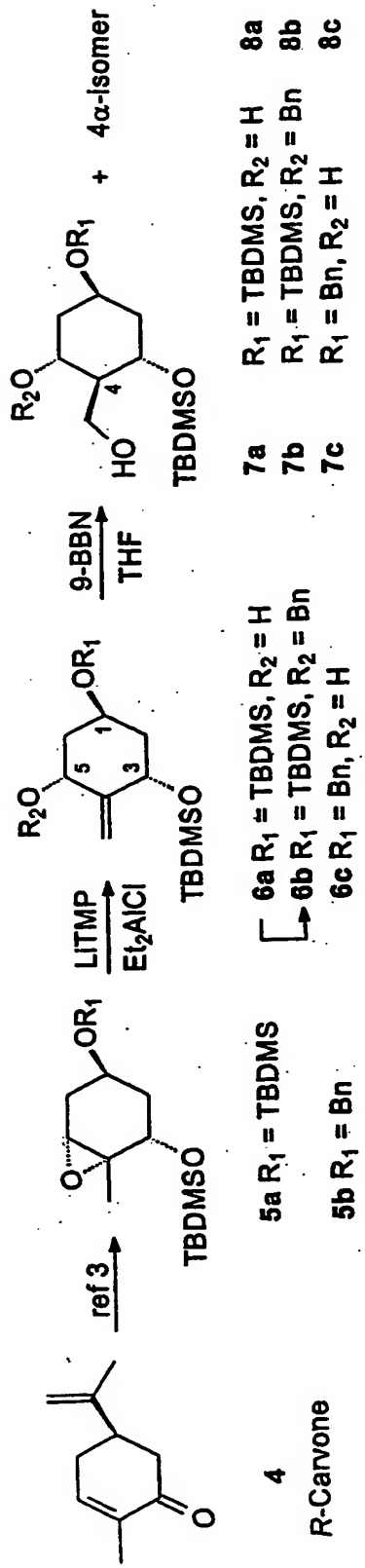

4
R-Carvone
ref 3
5a R1 = TBDMS
5b R1 = Bn
TBDMSO
LITMP
Et2AlCl
6a R1 = TBDMS, R2 = H
6b R1 = TBDMS, R2 = Bn
6c R1 = Bn, R2 = H
9-BBN
THF
7a R1 = TBDMS, R2 = H 8a
7b R1 = TBDMS, R2 = Bn 8b
7c R1 = Bn, R2 = H 8c
+ 4α-isomer

FIG. 7

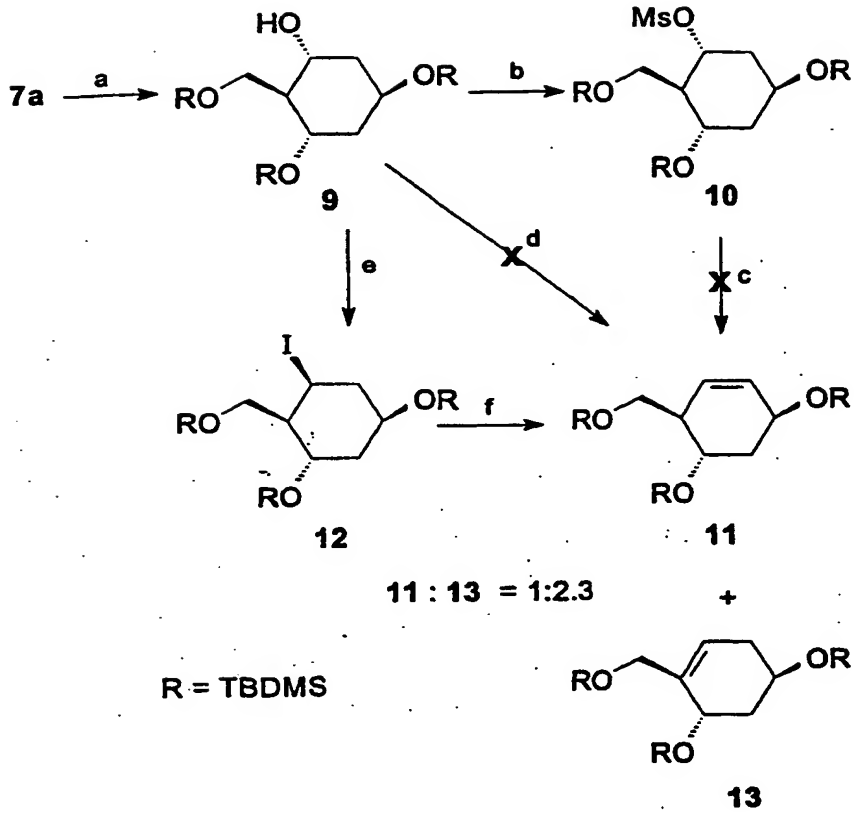

7a
a
HO
RO
OR
RO
9
b
MsO
RO
OR
RO
10
d
c
e
I
RO
OR
RO
12
f
RO
OR
RO
11
11 : 13 = 1:2.3
+
R = TBDMS
RO
OR
RO
13

FIG. 8

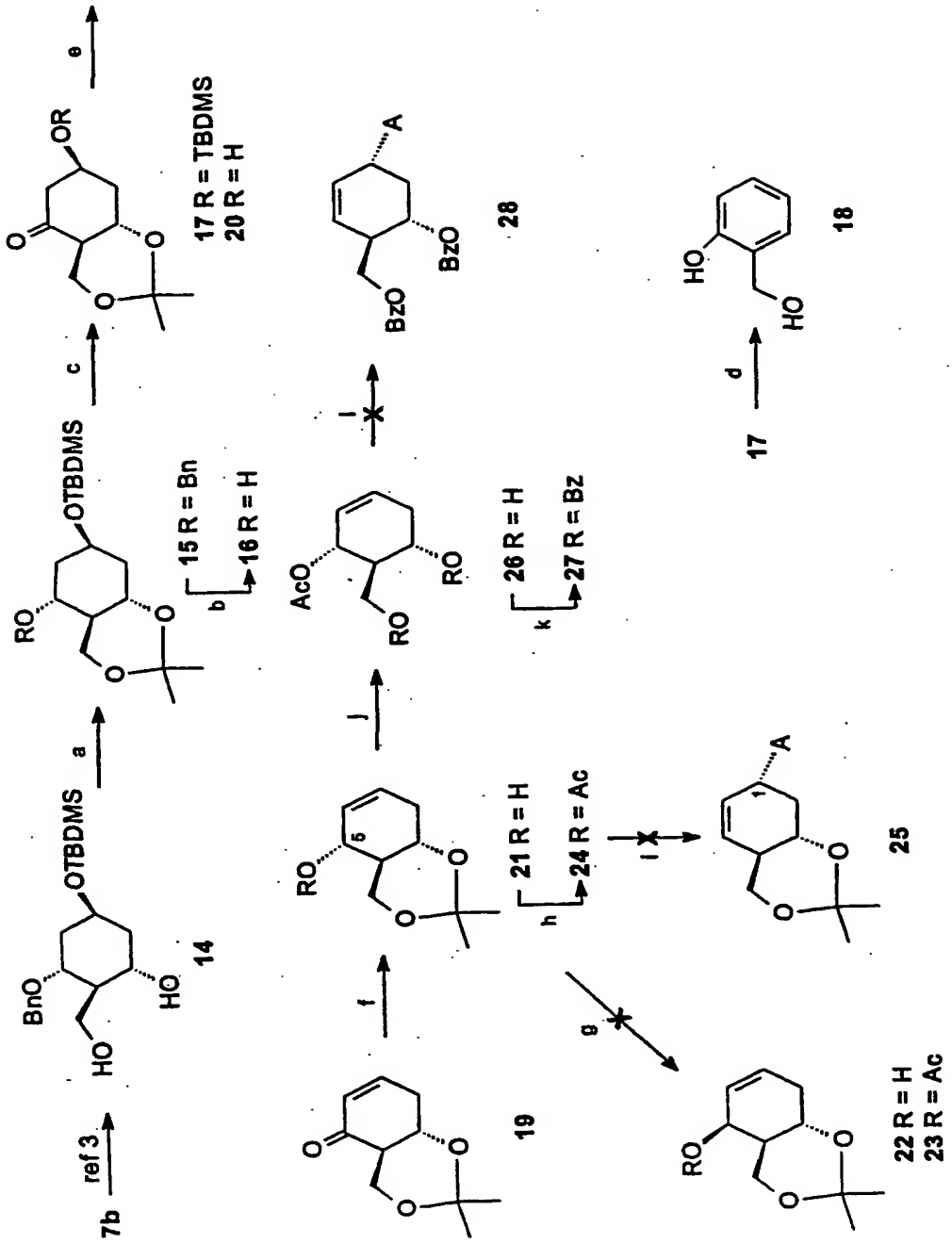

7b
ref 3
14
19
17 R = TBDMS
20 R = H
15 R = Bn
16 R = H
21 R = H
24 R = Ac
26 R = H
27 R = Bz
28
17
18
25
22 R = H
23 R = Ac
a
b
c
d
e
f
g
h
i
j
k
l

FIG. 9

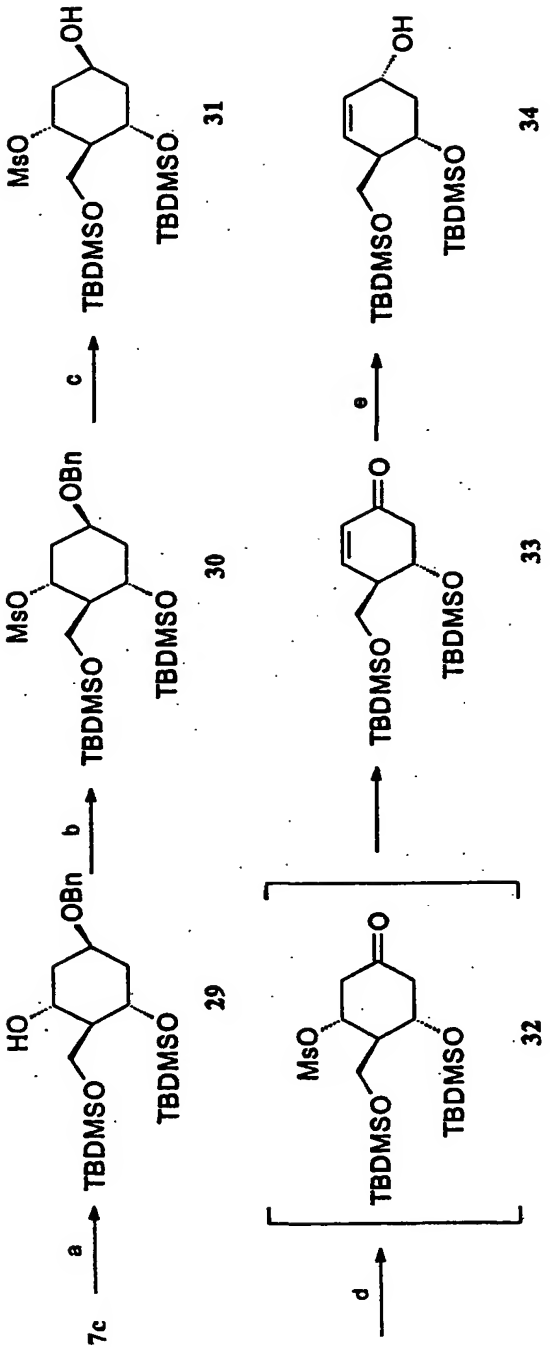

7c
a
HO
OBn
TBDMSO
TBDMSO
29
b
MsO
OBn
TBDMSO
TBDMSO
30
c
MsO
OH
TBDMSO
TBDMSO
31
d
MsO
O
TBDMSO
TBDMSO
32
e
O
TBDMSO
TBDMSO
33
OH
TBDMSO
TBDMSO
34

FIG. 10

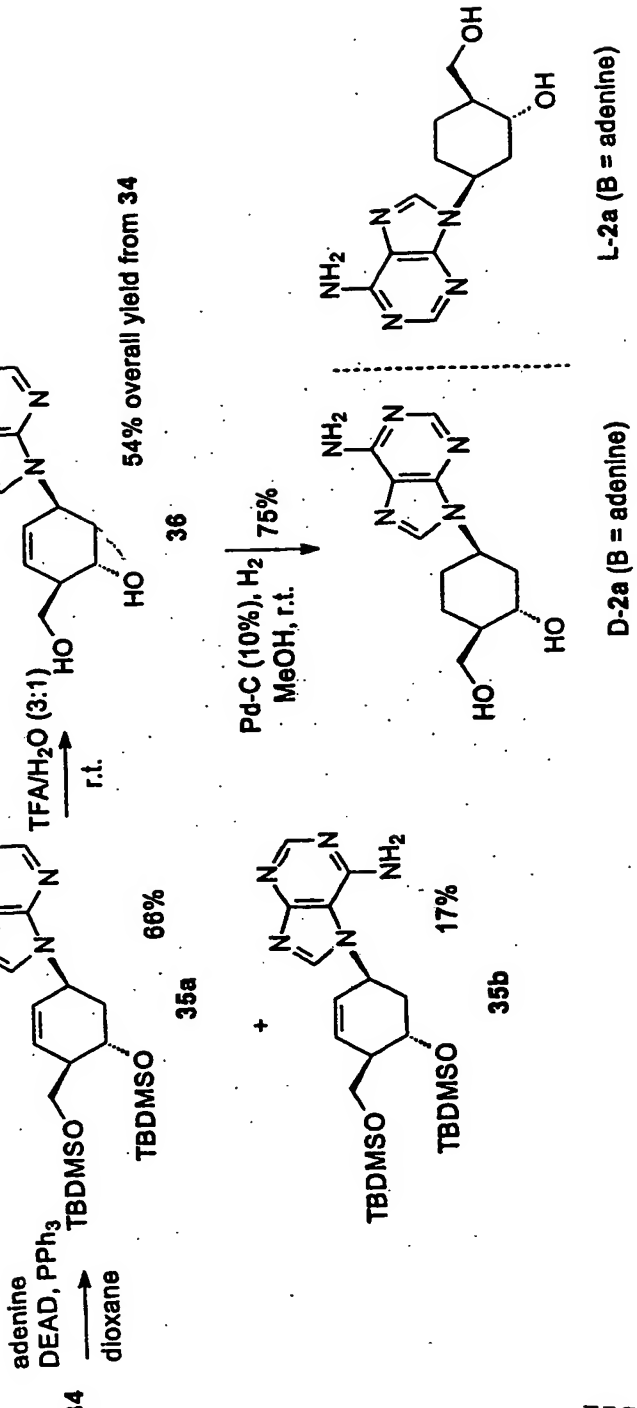

adenine
DEAD, PPh3
dioxane
34
TBDMSO
TBDMSO
35a
66%
+
TBDMSO
TBDMSO
35b
17%
TFA/H2O (3:1)
r.t.
54% overall yield from 34
36
HO
HO
Pd-C (10%), H2
MeOH, r.t.
75%
D-2a (B = adenine)
L-2a (B = adenine)
NH2
OH
N

FIG. 11